

**IMIDAZOLE DERIVATIVES AND THEIR USE AS CYTOKINE INHIBITORS****Patent number:** JP7503017T**Publication date:** 1995-03-30**Inventor:****Applicant:****Classification:****- international:** C07D401/04; A61K31/44; A61K31/47; A61K31/505;  
C07D403/04; C07D409/14**- european:** C07D401/04; C07D413/14**Application number:** JP19930512741T 19930113**Priority number(s):** US19920819551 19920113; US19920867249 19920410;  
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Novel 2,4,5-triarylimidazole compounds and compositions for use in therapy.

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<p>(21) International Application Number: PCT/US93/00674 (22) International Filing Date: 13 January 1993 (13.01.93) (30) Priority data: 07/819,551 13 January 1992 (13.01.92) US 07/867,249 10 April 1992 (10.04.92) US (60) Parent Applications or Grants (63) Related by Continuation US 07/867,249 (CIP) Filed on 10 April 1992 (10.04.92) US 07/819,551 (CIP) Filed on 13 January 1992 (13.01.92) (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Jerry, Leroy [US/US]; 611 Forest Road, Wayne, PA 19087 (US). GALLAGHER, Timothy, Francis [US/US]; 255 Manor Road, Harleysville, PA 19438 (US). LEE, John, C. [US/US]; 245 Gulph Hills Road, Radnor, PA 19087 (US). WHITE, John, Richard [GB/US]; 332 Jennifer Drive, Coatesville, PA 19320 (US).</p>		<p>(74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, SK, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: IMIDAZOLE DERIVATIVES AND THEIR USE AS CYTOKINE INHIBITORS (57) Abstract Novel 2,4,5-triarylimidazole compounds and compositions for use in therapy.</p>		

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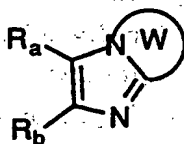
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## IMIDAZOLE DERIVATIVES AND THEIR USE AS CYTOKINE INHIBITORS

This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

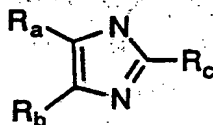
## BACKGROUND OF THE INVENTION:

There has been much interest in the past few years in compounds which are cytokine-inhibitors, for use in treating disease states which are associated with the excessive or unregulated production of cytokines. Compounds of the general formula (A):



(A)

wherein  $R_a$  is pyridyl,  $R_b$  is optionally substituted phenyl and  $W$  is a partially or fully unsaturated fused 5- or 6-membered heterocyclic ring, such as pyrrolyl, pyridyl, dihydropyrrolyl, dihydropyridinyl, dihydrothiazolyl or tetrahydro-triazinyl, are inhibitors of the cytokines IL-1 and TNF (see WO88/01169, WO90/15534, WO91/00092, WO92/10190, WO92/10498 and WO92/12154, published after the filing of this application). In addition, these compounds are also inhibitors of the enzyme 5-lipoxygenase. We have now surprisingly found that if the ring  $W$  is replaced by certain substituents at the 2-position, cytokine-inhibitory activity is maintained. Such compounds are generically 2-substituted-4-aryl-5-heteroaryl-imidazoles. Compounds within this class have already been extensively investigated, as anti-inflammatory agents, acting principally as cyclo-oxygenase inhibitors, as described in, for instance, US patents 3,707,405 and 3,929,807. The latter discloses compounds of the general formula (B):



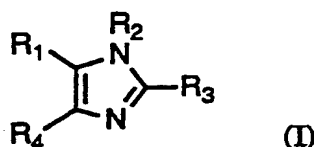
(B)

wherein one of  $R_a$  and  $R_b$  is optionally substituted phenyl and the other is a 6-membered heterocyclic ring with 1 or 2 nitrogen atoms and  $R_c$  represents lower alkyl, cycloalkyl or phenyl optionally substituted by halogen, lower alkyl or lower alkoxy, in particular the compound 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-pyridyl)-imidazole. These compounds are said to have

anti-inflammatory, analgesic and antipyretic activity. There is however no mention that these compounds may be cytokine inhibitors.

# FULL DESCRIPTION OF THE INVENTION:

5 Accordingly, the present invention provides a compound of formula (I):



wherein:

- 10  $R_1$  is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolyl, 1-imidazolyl or 1-benzimidazolyl which is optionally substituted with one or two substituents each of which is independently selected from C<sub>1-4</sub> alkyl, halo, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, NH<sub>2</sub>, mono- or di-C<sub>1-6</sub>-alkylamino or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>22</sub>;
- 15  $R_2$  is R<sub>8</sub> or -OR<sub>12</sub>;  
 $R_3$  is -X<sub>a</sub>P(Z)(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> or Q-(Y<sub>1</sub>)<sub>t</sub>;  
 Q is an aryl or heteroaryl group;  
 t is an integer of 1 to 3;  
 X<sub>a</sub> is -NR<sub>8</sub>-, -O-, -S- or a C<sub>1-10</sub> alkylene chain optionally substituted by C<sub>1-4</sub> alkyl and optionally interrupted by -NR<sub>8</sub>-, -O- or -S-;
- 20 X<sub>b</sub> is -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>-, -NR<sub>8</sub>-, -O- or -S-;  
 Z is oxygen or sulfur;  
 n is 0 or an integer from 1 to 10;  
 Y<sub>1</sub> is independently selected from hydrogen, C<sub>1-5</sub> alkyl, halo-substituted C<sub>1-5</sub> alkyl, halogen, -X<sub>a</sub>-P(Z)-(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub>;
- 25 Y<sub>2</sub> is -OR<sub>8</sub>-, -NO<sub>2</sub>-, -S(O)<sub>m'</sub>R<sub>11</sub>-, -SR<sub>8</sub>-, -S(O)<sub>m'</sub>OR<sub>8</sub>-, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>8</sub>R<sub>9</sub>-, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>-, -C(O)R<sub>8</sub>-, -CO<sub>2</sub>R<sub>8</sub>-, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>-, -ZC(O)R<sub>8</sub>-, -CN-, -C(Z)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>C(Z)R<sub>8</sub>-, -C(Z)NR<sub>8</sub>OR<sub>9</sub>-, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>-, -N(OR<sub>21</sub>)C(Z)NR<sub>8</sub>R<sub>9</sub>-, -N(OR<sub>21</sub>)C(Z)R<sub>8</sub>-, -C(=NOR<sub>21</sub>)R<sub>8</sub>-, -NR<sub>10</sub>C(=NR<sub>15</sub>)SR<sub>11</sub>-, -NR<sub>10</sub>C(=NR<sub>15</sub>)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)SR<sub>11</sub>-, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>C(O)C(O)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>C(O)C(O)OR<sub>10</sub>-, -C(=NR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>-, -C(=NOR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>-, -C(=NR<sub>13</sub>)ZR<sub>11</sub>-, -OC(Z)NR<sub>8</sub>R<sub>9</sub>-, -NR<sub>10</sub>S(O)<sub>m</sub>CF<sub>3</sub>-, -NR<sub>10</sub>C(Z)OR<sub>10</sub>-, 5-(R<sub>18</sub>)-1,2,4-oxadiazol-3-yl or 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl;
- 35 m' is 1 or 2;

- $n'$  is an integer from 1 to 10;
- $R_4$  is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano,  $-C(Z)NR_7R_{17}$ ,  $-C(Z)OR_{23}$ ,  $-(CR_{10}R_{20})_mCOR_{36}$ ,  $-SR_5$ ,  $-SOR_5$ ,  $-OR_{36}$ , halo-substituted- $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl,  $-ZC(Z)R_{36}$ ,  $-NR_{10}C(Z)R_{23}$ , or  $-(CR_{10}R_{20})_mNR_{10}R_{20}$  and which, for other positions of substitution, is halo, cyano,  $-C(Z)NR_{16}R_{26}$ ,  $-C(Z)OR_8$ ,  $-(CR_{10}R_{20})_mCOR_8$ ,  $-S(O)_mR_8$ ,  $-OR_8$ , halo-substituted- $C_{1-4}$  alkyl,  $-C_{1-4}$  alkyl,  $-(CR_{10}R_{20})_mNR_{10}C(Z)R_8$ ,  $-NR_{10}S(O)_mR_{11}$ ,  $-NR_{10}S(O)_mNR_7R_{17}$  wherein  $m$  is 1 or 2,  $-ZC(Z)R_8$  or  $-(CR_{10}R_{20})_mNR_{16}R_{26}$ ;
- $m$  is 0, or the integer 1 or 2;
- $R_5$  is hydrogen,  $C_{1-4}$  alkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl or  $NR_7R_{17}$ , excluding the moieties  $-SR_5$  being  $-SNR_7R_{17}$  and  $-SOR_5$  being  $-SOH$ ;
- $R_6$  is  $C_{1-4}$  alkyl, halo-substituted- $C_{1-4}$  alkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl or C3-5 cycloalkyl;
- $R_7$  and  $R_{17}$  is each independently selected from hydrogen or  $C_{1-4}$  alkyl or  $R_7$  and  $R_{17}$  together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or  $NR_{22}$ ;
- $R_8$  is hydrogen, heterocyclyl, heterocyclalkyl or  $R_{11}$ ;
- $R_9$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl, C3-7 cycloalkyl, C5-7 cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or  $R_8$  and  $R_9$  may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or  $NR_{12}$ ;
- $R_{10}$  and  $R_{20}$  is each independently selected from hydrogen or  $C_{1-4}$  alkyl;
- $R_{11}$  is  $C_{1-10}$  alkyl, halo-substituted  $C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl, C3-7 cycloalkyl, C5-7 cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- $R_{12}$  is hydrogen,  $-C(Z)R_{13}$  or optionally substituted  $C_{1-4}$  alkyl, optionally substituted aryl or optionally substituted aryl- $C_{1-4}$  alkyl;
- $R_{13}$  is hydrogen,  $C_{1-10}$  alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- $R_{14}$  and  $R_{24}$  is each independently selected from hydrogen, alkyl, nitro or cyano;  $R_{15}$  is hydrogen, cyano,  $C_{1-4}$  alkyl, C3-7 cycloalkyl or aryl;
- $R_{16}$  and  $R_{26}$  is each independently selected from hydrogen or optionally substituted  $C_{1-4}$  alkyl, optionally substituted aryl or optionally substituted aryl- $C_{1-4}$  alkyl, or together with the nitrogen which they are

- attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>12</sub> ;
- R<sub>18</sub> and R<sub>19</sub> is each independently selected from hydrogen, C<sub>1-4</sub> alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;
- 5 R<sub>21</sub> is hydrogen, a pharmaceutically acceptable cation, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl C<sub>1-4</sub> alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C<sub>1-10</sub> alkoyl ;
- R<sub>22</sub> is R<sub>10</sub> or C(Z)-C<sub>1-4</sub> alkyl;
- 10 R<sub>23</sub> is C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, or C<sub>3-5</sub> cycloalkyl;
- R<sub>36</sub> is hydrogen or R<sub>23</sub>;
- or a pharmaceutically acceptable salt thereof;
- and excluding 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-pyridyl)imidazole.

- 15 Sutable R<sub>1</sub> moieties include 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinolyl, 1-imidazolyl and 1-benzimidazolyl, of which 4-pyridyl, 4-pyrimidinyl and 4-quinolyl, especially 4-pyridyl, are preferred. A preferred substituent for all R<sub>1</sub> moieties is C<sub>1-4</sub> alkyl, in particular methyl. More preferred as a substituted R<sub>1</sub> moiety is the 4-pyridyl derivative substituted
- 20 at the 2-position with C<sub>1-4</sub> alkyl, especially 2-methyl-4-pyridyl. Also preferred is the 4-pyrimidinyl derivative substituted at the 2-position with C<sub>1-4</sub> alkyl or NR<sub>10</sub>R<sub>20</sub>.

Preferably, R<sub>2</sub> is hydrogen or C<sub>1-10</sub> alkyl, more preferably, hydrogen or methyl.

- 25 Preferably, the R<sub>3</sub> moieties is an (un)substituted aryl or heteroaryl moiety Q, also referred to as Q-(Y<sub>1</sub>)<sub>t</sub>. Preferably, when Q is an aryl, specifically phenyl, and when Q is a heteroaryl, preferred groups include pyrrole, pyridine, or pyrimidine. More preferred is Q as phenyl. All preferred moieties are independently substituted by (Y<sub>1</sub>)<sub>t</sub>, wherein t is an integer of 1
- 30 to 3. Preferably t is 1 or 2. More preferably, when R<sub>3</sub> is monosubstituted phenyl, the substituent is located at the 4-position.

- Suitably the aryl or heteroaryl moiety of Q is substituted by up to three substituents Y<sub>1</sub> each of which is independently selected from C<sub>1-5</sub> alkyl, halo-substituted C<sub>1-5</sub> alkyl, halogen, -X<sub>a</sub>-P(Z)-(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub>
- 35 wherein Y<sub>2</sub> is -OR<sub>8</sub>, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sub>11</sub>, -SR<sub>8</sub>, -S(O)<sub>m</sub>OR<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>, -C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>, -ZC(O)R<sub>8</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -C(Z)NR<sub>8</sub>OR<sub>9</sub>, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -N(OR<sub>21</sub>)C(Z)NR<sub>8</sub>R<sub>9</sub>, -N(OR<sub>21</sub>)C(Z)R<sub>8</sub>, -C(=NOR<sub>21</sub>)R<sub>8</sub>,



$-\text{NR}_{10}\text{C}(=\text{NR}_{15})\text{SR}_{11}$ ,  $-\text{NR}_{10}\text{C}(=\text{NR}_{15})\text{NR}_8\text{R}_9$ ,  $-\text{NR}_{10}\text{C}(=\text{CR}_{14}\text{R}_{24})\text{SR}_{11}$ ,  
 $-\text{NR}_{10}\text{C}(=\text{CR}_{14}\text{R}_{24})\text{NR}_8\text{R}_9$ ,  $-\text{NR}_{10}\text{C}(\text{O})\text{C}(\text{O})\text{NR}_8\text{R}_9$ ,  $-\text{NR}_{10}\text{C}(\text{O})\text{C}(\text{O})\text{OR}_{10}$ ,  
 $-\text{C}(=\text{NR}_{13})\text{NR}_8\text{R}_9$ ,  $-\text{C}(=\text{NOR}_{13})\text{NR}_8\text{R}_9$ ,  $-\text{C}(=\text{NR}_{13})\text{ZR}_{11}$ ,  $-\text{OC}(\text{Z})\text{NR}_8\text{R}_9$ ,  
 $-\text{NR}_{10}\text{S}(\text{O})_m\text{CF}_3$ ,  $-\text{NR}_{10}\text{C}(\text{Z})\text{OR}_{10}$ , 5-( $\text{R}_{18}$ )-1,2,4-oxadiazol-3-yl or 4-( $\text{R}_{12}$ )-5-  
 5 (R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl; m' is 1 or 2; R<sub>9</sub> is hydrogen, C<sub>1-10</sub>  
 alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> cycloalkenyl, aryl,  
 arylalkyl, heteroaryl or heteroarylalkyl or R<sub>8</sub> and R<sub>9</sub> may together with the  
 nitrogen to which they are attached form a heterocyclic ring of 5 to 7  
 members which ring optionally contains an additional heteroatom selected  
 10 from oxygen, sulfur or NR<sub>12</sub>; R<sub>14</sub> and R<sub>24</sub> is each independently selected from  
 hydrogen, alkyl, nitro or cyano; R<sub>15</sub> is hydrogen, cyano, C<sub>1-4</sub> alkyl, C<sub>3-7</sub>  
 cycloalkyl or aryl; R<sub>18</sub> and R<sub>19</sub> is each independently selected from hydrogen,  
 C<sub>1-4</sub> alkyl, substituted alkyl, optionally substituted aryl, arylalkyl or together  
 with the carbon to which they are attached denote a double bonded oxygen or  
 15 sulfur, i.e., a C=O or C=S; and R<sub>21</sub> is hydrogen, a pharmaceutically acceptable  
 cation, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heterocyclic,  
 heteroarylalkyl, aroyl, alkoyl.

Preferred substituents Y<sub>1</sub> for use in R<sub>3</sub> include halogen, C<sub>1-5</sub> alkyl  
 and  $-(\text{CR}_{10}\text{R}_{20})_n\text{Y}_2$  wherein Y<sub>2</sub> is -OR<sub>8</sub>, -NO<sub>2</sub>,  $-\text{S}(\text{O})_m\text{R}_{11}$ , -SR<sub>8</sub>,  
 20  $-\text{S}(\text{O})_m\text{NR}_8\text{R}_9$ , -NR<sub>8</sub>R<sub>9</sub>,  $-\text{O}(\text{CR}_{10}\text{R}_{20})_n\text{NR}_8\text{R}_9$ , -C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>,  
 $-\text{CO}_2(\text{CR}_{10}\text{R}_{20})_n$ , CONR<sub>8</sub>R<sub>9</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>,  $-\text{NR}_{10}\text{S}(\text{O})_m\text{R}_{11}$ ,  
 $-\text{NR}_{10}\text{C}(\text{Z})\text{R}_8$ ,  $-\text{NR}_{10}\text{C}(\text{Z})\text{NR}_8\text{R}_9$ ,  $-\text{C}(\text{Z})\text{NR}_8\text{OR}_9$ ,  $-\text{N}(\text{OR}_{21})\text{C}(\text{Z})\text{NR}_8\text{R}_9$ ,  
 $-\text{NR}_{10}\text{C}(=\text{NR}_{15})\text{NR}_8\text{R}_9$ ,  $-\text{C}(=\text{NOR}_{13})\text{NR}_8\text{R}_9$ , 5-( $\text{R}_{18}$ )-1,2,4-oxadiazol-3-yl and  
 4-( $\text{R}_{12}$ )-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl.

25 Preferred substituents Y<sub>1</sub> for use in R<sub>3</sub> when the aryl or heteroaryl  
 group Q is mono-substituted include  $-(\text{CR}_{10}\text{R}_{20})_n\text{Y}_2$  wherein: n is 0, 1, 2 or  
 3, preferably 0 or 1; and Y<sub>2</sub> is -OR<sub>8</sub>, especially where R<sub>8</sub> is hydrogen or  
 C<sub>1-10</sub> alkyl; -NO<sub>2</sub>;  $-\text{S}(\text{O})_m\text{R}_{11}$ , especially where R<sub>11</sub> is C<sub>1-10</sub> alkyl; -SR<sub>8</sub>,  
 especially where R<sub>8</sub> is C<sub>1-10</sub> alkyl;  $-\text{S}(\text{O})_m\text{NR}_8\text{R}_9$ , especially where R<sub>8</sub> and  
 30 R<sub>9</sub> is each hydrogen or C<sub>1-10</sub> alkyl or R<sub>8</sub> and R<sub>9</sub> together with the nitrogen  
 to which they are attached form a 5 to 7 membered ring which optionally  
 includes another heteroatom selected from oxygen, sulfur or NR<sub>12</sub> and m is  
 2; n' is 1 to 10; -NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is each hydrogen,  
 methyl or benzyl or R<sub>8</sub> and R<sub>9</sub> together with the nitrogen to which they are  
 35 attached form a 5 to 7 membered ring which optionally includes another  
 heteroatom selected from oxygen, sulfur or NR<sub>12</sub>;  $-\text{O}(\text{CR}_{10}\text{R}_{20})_n\text{NR}_8\text{R}_9$ ,  
 especially where R<sub>8</sub> and R<sub>9</sub> is each C<sub>1-10</sub> alkyl; -C(O)R<sub>8</sub>, especially where  
 R<sub>8</sub> is hydrogen or C<sub>1-10</sub> alkyl; -CO<sub>2</sub>R<sub>8</sub>, especially where R<sub>8</sub> is hydrogen or  
 C<sub>1-10</sub> alkyl;  $-\text{CO}_2(\text{CR}_{10}\text{R}_{20})_n$ , CONR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is

- hydrogen or C<sub>1-10</sub> alkyl; -CN; -C(Z)NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is hydrogen or C<sub>1-10</sub> alkyl; -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, especially where R<sub>10</sub> is hydrogen or C<sub>1-10</sub> alkyl and R<sub>11</sub> is C<sub>1-10</sub> alkyl or a halosubstituted; -NR<sub>10</sub>C(Z)R<sub>8</sub>, especially where R<sub>8</sub> is C<sub>1-10</sub> alkyl and R<sub>10</sub> is hydrogen and Z is oxygen;
- 5 -C(Z)NR<sub>8</sub>OR<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is each hydrogen and Z is oxygen; -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is each hydrogen or C<sub>1-10</sub> alkyl and Z is oxygen; -N(OR<sub>21</sub>)C(Z)NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> especially where R<sub>8</sub>, R<sub>9</sub> and R<sub>21</sub> is each hydrogen or C<sub>1-10</sub> alkyl and Z is oxygen; -C(=NOR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub>, R<sub>9</sub> and R<sub>13</sub> is each hydrogen;
- 10 -NR<sub>10</sub>C(=NR<sub>15</sub>)NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is hydrogen, C<sub>1-10</sub> alkyl or arylalkyl and R<sub>15</sub> is cyano; and 5-(R<sub>18</sub>)-1,2,4-oxadizaol-3-yl and 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R<sub>12</sub> is hydrogen and R<sub>18</sub> and R<sub>19</sub> is each hydrogen or C<sub>1-10</sub> alkyl or together are oxo.
- 15 Preferred substituents for use in R<sub>3</sub> when the aryl or heteroaryl group Q is disubstituted include those hereinbefore listed for use when Q is mono-substituted and, as further substituent(s), halogen and C<sub>1-10</sub> alkyl. When R<sub>3</sub> is phenyl substituted with two or three substituents, the alkyl moieties preferably have from one to three carbons, more preferably one. Preferred
- 20 ring positions for two substituents are the 3- and 4-positions and, for three substituents, the 3-, 4- and 5- positions. The substituent at the 3- and 5-positions is preferably C<sub>1-2</sub> alkyl, such as methyl, or halogen, such as bromo, fluoro or chloro, while the substituent at the 4-position is preferably hydroxyl.
- More preferably, for R<sub>3</sub> substituents wherein Y<sub>1</sub> is (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub>, n
- 25 is 0 or 1 and Y<sub>2</sub> is -OH, -S(O)<sub>m</sub>R<sub>11</sub>, especially where R<sub>11</sub> is C<sub>1-10</sub> alkyl; -SR<sub>8</sub>, especially where R<sub>8</sub> is C<sub>1-10</sub> alkyl; -NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is hydrogen, alkyl, aryl alkyl, or aryl or R<sub>8</sub> and R<sub>9</sub> together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl or morpholinyl ring, more preferably the R<sub>8</sub> and R<sub>9</sub> terms in the NR<sub>8</sub>R<sub>9</sub>
- 30 moiety are hydrogen, methyl or benzyl; -CO<sub>2</sub>R<sub>8</sub>, especially where R<sub>8</sub> is hydrogen or C<sub>1-10</sub> alkyl; -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, especially where R<sub>8</sub> and R<sub>9</sub> is each hydrogen or C<sub>1-10</sub> alkyl; -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, especially where R<sub>10</sub> is hydrogen and R<sub>11</sub> is C<sub>1-10</sub> alkyl or 5-(R<sub>18</sub>)-1,2,4-oxadizaol-3-yl and 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R<sub>12</sub> is hydrogen and R<sub>18</sub>
- 35 and R<sub>19</sub> is hydrogen or C<sub>1-10</sub> alkyl or together are oxo.

Most preferably, Y<sub>1</sub> is methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, N,N-dimethylaminomethyl, N-benzyl-N-

methylaminomethyl, N-morpholinomethyl, methanesulfonamido, sulphonamidomethyl, 5-methyl-4,5-dihydro-1,2,4-oxadiazol-3-yl or 5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, such as in R<sub>5</sub>, R<sub>8</sub>, R<sub>9</sub>, or R<sub>11</sub> the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in Y<sub>2</sub> as C(Z)NR<sub>8</sub>OR<sub>9</sub>, NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, or OR<sub>8</sub>. As used herein, "optionally substituted" unless specified refers to such groups as halogen, hydroxyl, alkoxy, S(O)<sub>m</sub> alkyl, amino, mono & di-substituted amino, such as a NR<sub>7</sub>R<sub>17</sub> group, alkyl or cycloalkyl, i.e. such as in optionally substituted aryl or optionally substituted arylalkyl.

When R<sub>3</sub> includes a X<sub>a</sub>-P(Z)(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> group linked either directly to the imidazole ring or indirectly *via* an aryl or heteroaryl group, X<sub>a</sub> is suitably oxygen or C<sub>1-4</sub> alkylene, optionally interrupted by oxygen, for instance -CH<sub>2</sub>OCH<sub>2</sub>- and Z and X<sub>b</sub> is each oxygen, such that the preferred groups include -OP(O)(OR<sub>13</sub>)<sub>2</sub> and -CH<sub>2</sub>OCH<sub>2</sub>-P(O)(OR<sub>13</sub>)<sub>2</sub>.

Preferred substitutions for R<sub>4</sub> when this is a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl moiety are one or two substituents each independently selected from halogen, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>36</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>10</sub>R<sub>20</sub>, and for other positions of substitution on these rings preferred substitution is halogen, -S(O)<sub>m</sub>R<sub>8</sub>, -OR<sub>8</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>16</sub>R<sub>26</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub> and -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>. More preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro, and -SR<sub>5</sub> and -SOR<sub>5</sub> wherein R<sub>5</sub> is preferably a C<sub>1-2</sub> alkyl, more preferably methyl; of which fluoro is especially preferred. Preferred substituents for the 3-position in phenyl and naphth-1-yl include: halogen, especially chloro; -OR<sub>8</sub>, especially C<sub>1-4</sub> alkoxy; amino; -NR<sub>10</sub>C(Z)R<sub>8</sub>, especially -NHCO(C<sub>1-10</sub> alkyl); and -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, especially -NH<sub>2</sub>SO<sub>2</sub>(C<sub>1-10</sub> alkyl). Preferably, the R<sub>4</sub> moiety is an unsubstituted or substituted phenyl moiety. More preferably, R<sub>4</sub> is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C<sub>1-4</sub> alkoxy, methanesulfonamido or acetamido.

In a preferred subgenus of compounds of formula (I), R<sub>1</sub> is 4-pyridyl, 2-alkyl-4-pyridyl or 4-quinolyl; R<sub>2</sub> is hydrogen or methyl; R<sub>3</sub> is phenyl or phenyl substituted, preferably at the 4-position, with a substituent selected from -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub> wherein Y<sub>2</sub> is wherein n is 0, 1, 2 or 3 and Y<sub>2</sub> is -OR<sub>8</sub>, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sub>11</sub>, -SR<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>,

-C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>,  
 -C(Z)NR<sub>8</sub>OR<sub>9</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>,  
 -C(=NOR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)NR<sub>8</sub>R<sub>9</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadiazol-3-yl,  
 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl, a 3,5-dimethyl or  
 5 dibromo-4-hydroxyl grouping; and R<sub>4</sub> is phenyl or phenyl substituted at the  
 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro,  
 C<sub>1-4</sub> alkoxy, methanesulfonamido or acetamido.

In a more preferred subgenus, R<sub>1</sub> is 4-pyridyl, 2-methyl-4-pyridyl or  
 4-quinolyl; R<sub>2</sub> is hydrogen or methyl; R<sub>3</sub> is phenyl substituted at the 4-  
 10 position with C<sub>1-10</sub> alkylthio, C<sub>1-10</sub> alkylsulfinyl, C<sub>1-10</sub> alkylsulfonyl,  
 N,N-di(C<sub>1-10</sub> alkyl)amino C<sub>1-2</sub> alkyl, N-alkyl-N-C<sub>1-10</sub> alkylamino C<sub>1-2</sub>  
 alkyl, N-morpholino C<sub>1-2</sub> alkyl, C<sub>1-10</sub> alkylsulfonamido, sulphonamido C<sub>1-2</sub>  
 alkyl, 5-C<sub>1-10</sub> alkyl-4,5-dihydro-1,2,4-oxadiazol-3-yl or 5,5-di(C<sub>1-10</sub> alkyl)-  
 4,5-dihydro-1,2,4-oxadiazol-3-yl; and R<sub>4</sub> is phenyl or phenyl substituted at  
 15 the 4-position with fluoro and/or substituted at the 3-position with fluoro,  
 chloro, C<sub>1-4</sub> alkoxy, methane-sulfonamido or acetamido.

Suitable pharmaceutically acceptable salts are well known to those  
 skilled in the art and include basic salts of inorganic and organic acids, such  
 as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid,  
 20 methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid,  
 tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid,  
 maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid.  
 In addition, pharmaceutically acceptable salts of compounds of formula (I)  
 may also be formed with a pharmaceutically acceptable cation, for instance,  
 25 if a substituent Y<sub>1</sub> in R<sub>3</sub> comprises a carboxy group. Suitable pharma-  
 ceutically acceptable cations are well known to those skilled in the art and  
 include alkaline, alkaline earth, ammonium and quaternary ammonium  
 cations.

The following terms, as used herein, refer to:

- 30 • "halo" - all halogens, that is chloro, fluoro, bromo and iodo;
- "C<sub>1-10</sub>alkyl" or "alkyl" - both straight and branched chain radicals  
 of 1 to 10 carbon atoms, unless the chain length is otherwise limited,  
 including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-  
 butyl, *iso*-butyl, *tert*-butyl, and the like;
- 35 • "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as  
 "heteroaryloxy") - a 5-10 membered aromatic ring system in which one or  
 more rings contain one or more heteroatoms selected from the group

consisting of N, O or S, such as, but not limited, to pyrrole, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole;

• "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine or pyrazolidine;

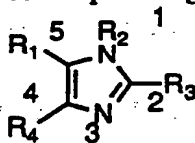
• "aroyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivatives, such as benzyl and the like;

• "alkoyl" - a C(O)C<sub>1-10</sub>alkyl wherein the alkyl is as defined above;

• "sulfinyl" - the oxide (SO) of the corresponding sulfide whilst the term "thio" refers to the sulfide.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

For the purposes herein of nomenclature, the compounds of formula (I) are named by their position corresponding to:



Especially preferred compounds of formula (I) include:

- 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-Fluorophenyl)-2-(4-ethylthiophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
- 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 4-(4-Fluorophenyl)-2-(4-ethylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 4-(3-Chlorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 2-[4-(N-Methyl-N-benzyl)aminomethylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)imidazole;
- 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylsulfinylphenyl)imidazole;
- 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-quinolyl)imidazole;

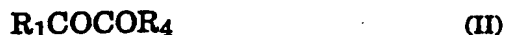
2-[4-(N-Morpholino)methylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-  
imidazole; and  
pharmaceutically acceptable salts thereof.

5 Other preferred compounds of formula (I) include:

- 2-[(4-N,N-Dimethyl)aminomethylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-  
imidazole;  
2-(4-Methanesulfonamidophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;  
4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-quinolyl)imidazole;  
10 4-(3-Chlorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;  
4-(3-Methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;  
4-(3-Methoxyphenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;  
4-(3-Methanesulfonamidophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-  
imidazole;  
15 4-(3-Methanesulfonamidophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-  
imidazole;  
3-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]phenyl-5,5-dimethyl-4,5-  
dihydro-1,2,4-oxadiazole; or  
3-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]phenyl-5-methyl-4,5-  
20 dihydro-1,2,4-oxadiazole; and  
pharmaceutically acceptable salts thereof.

Compounds of formula (I) are imidazole derivatives which may be  
readily prepared using procedures well-known to those skilled in the art,  
25 and described in, for instance, Comprehensive Heterocyclic Chemistry, ed  
Katritzky and Rees, Pergamon Press, 1984, 5, 457-497, from starting  
materials which are either commercially available or can be prepared from  
such by analogy with well-known processes. A key step in many such  
syntheses is the formation of the central imidazole nucleus, to give  
30 compounds of formula (I). Suitable procedures are described in *inter alia* US  
patent nos. 3,707,475 and 3,940,486 which are herein incorporated by  
reference in their entirety. These patents describe the synthesis of  $\alpha$ -  
diketones and  $\alpha$ -hydroxyketones (benzoins) and their subsequent use in  
preparing imidazoles and N-hydroxyl imidazoles. Thereafter, further  
35 compounds of formula (I) may be obtained by manipulating substituents in  
any of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> using conventional functional group  
interconversion procedures.

In particular, in a first process, compounds of formula (I) may be  
prepared by condensing an  $\alpha$ -diketone of formula (II):



wherein  $R_1$  and  $R_4$  are as hereinbefore defined, or an equivalent thereof, with an aldehyde of the formula (III):



- 5 wherein  $R_3$  is as hereinbefore defined, or an equivalent thereof, and, if necessary, with ammonia or a source thereof, under imidazole-ring forming conditions.

Suitable equivalents of the  $\alpha$ -diketone are well known to those skilled in the art and include the corresponding  $\alpha$ -keto-oxime and  $\alpha$ -dioxime.

- 10 Suitable equivalents of the aldehyde of formula (III) are well known in the art and include the corresponding oxime and acetal.

Ammonia, or a source thereof, is preferably used in excess, with at least a dimolar amount being used in the case of the  $\alpha$ -diketone and at least an equimolar amount in the case of the  $\alpha$ -keto-oxime.

- 15 Suitable sources of ammonia include ammonium salts of organic carboxylic acids, such as an ammonium  $C_{1-6}$  alkanoate, for instance ammonium acetate and ammonium formate, preferably ammonium acetate, and carboxylic amides, in particular of formic acid, such as formamide. An ammonium salt is generally used in large excess and in the presence of an acid, such as a  $C_{1-6}$  carboxylic acid which acid may also be used as a solvent  
20 for the reaction. If formamide is used, this may be used in excess, as the reaction solvent. An alternative solvent such as ethanol or dimethyl sulphoxide (Lantos *et al*, J Het Chem, 19, 1375; 1982) may be used. An additional solvent may also be employed, for instance, dimethyl formamide  
25 may be used with formamide. The reaction is generally carried out at elevated temperatures, for instance under reflux conditions, and if desired, in a sealed vessel optionally under pressure and/or an inert gas atmosphere, for instance nitrogen.

- A further suitable source of ammonia is hydroxylamine, in which case  
30 the initially formed imidazole is an N-hydroxy-N-oxide imidazole. This may then be reduced to the corresponding N-hydroxy imidazole by treating with a suitable reducing agent such as sodium borohydride, in an appropriate solvent such as methanol, following the method of Akange and Allan, Chem and Ind, 5 Jan 1975, 38. The N-hydroxy imidazole may in turn be converted  
35 to an imidazole of formula (I) in which  $R_2$  is hydrogen by treatment with a conventional deoxygenating agent such as phosphorus trichloride or a trialkylphosphite such as trimethyl- or triethyl-phosphite. N-hydroxy-N-oxide imidazoles may be readily obtained by treating an  $\alpha$ -diketone of

formula (II) with an aldehyde of formula (II) with about two equivalents of hydroxylamine or the corresponding aldoxime and about one equivalent of hydroxylamine, under proton catalysis. Alternatively, the N-oxide may be obtained by the acid catalysed condensation of the corresponding  $\alpha$ -dioxime or  $\alpha$ -keto-oxime with an aldoxime of the aldehyde of formula (III).

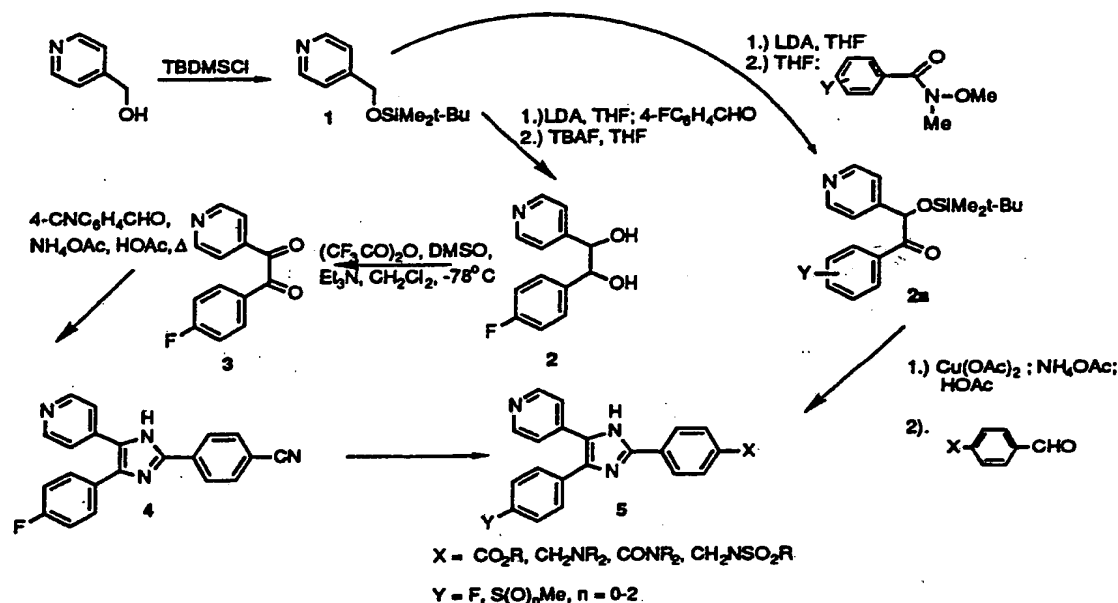
When the compound of formula (II) is an  $\alpha$ -keto-oxime derivative, it will be appreciated that the product initially obtained will be a compound of formula (I) in which  $R_2$  is hydroxyl which may be converted into a compound of formula (I) in which  $R_2$  is hydrogen as described above.

It will be appreciated by those skilled in the art that in some instances, it will not be necessary to provide a separate source of ammonia as the  $\alpha$ -diketone or aldehyde equivalent may already contain such a source. Examples of this include  $\alpha$ -dioxime or  $\alpha$ -keto-oxime and aldoxime.

The compounds of formula (II) may be obtained by applying well-known synthetic procedures, some of which are illustrated in schemes I and II. Although these illustrate syntheses in which  $R_4$  is either 4-pyridyl or 4-quinoliny, they may be equally applied to any of the other heteroaryl rings within the definition of  $R_4$  by appropriate choice of starting material.

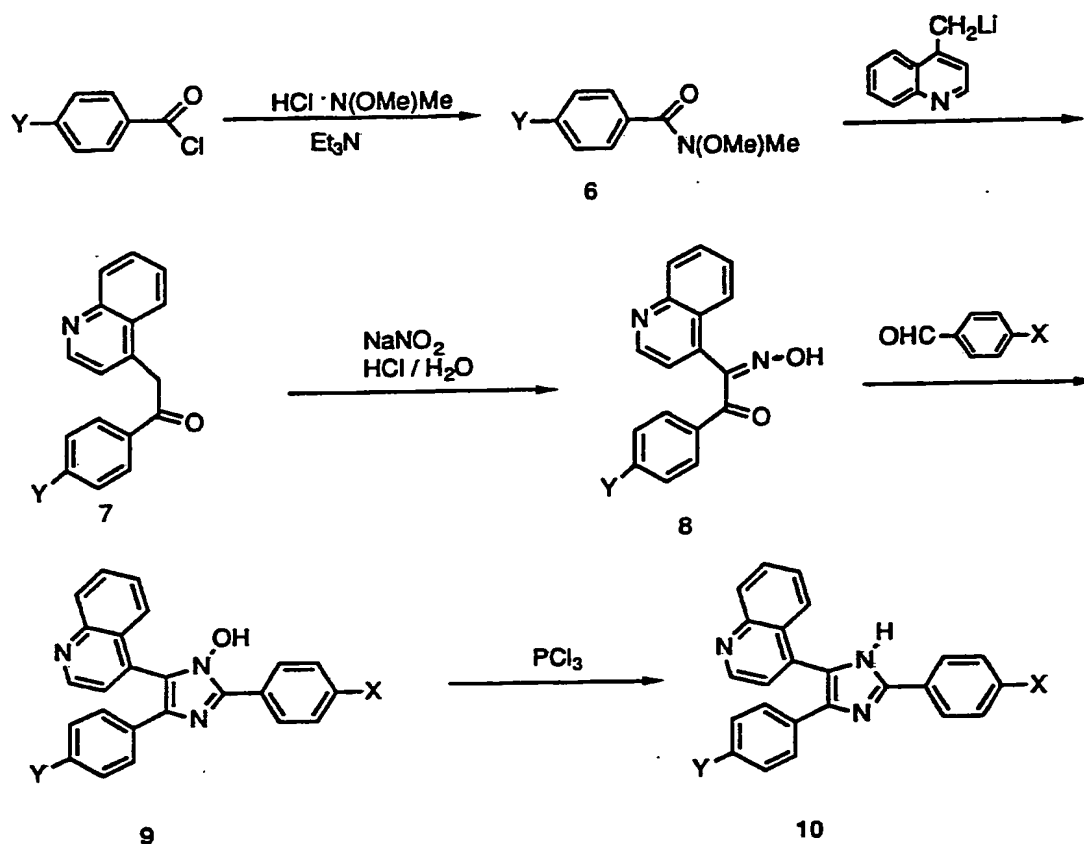
In Scheme I, the anion prepared from 1, by treatment with a strong base such as lithium di-*iso*-propylamide, is condensed with a substituted benz-aldehyde, to give, after removal of the protecting group, the diol 2. This may then be converted to the  $\alpha$ -diketone 3 by a Swern oxidation of which any number of potentially useful variations are known and may be used. The  $\alpha$ -diketone 3 is then cyclised to an imidazole 4, a compound of formula (I), by heating 3 with a substituted benzaldehyde in a mixture of ammonium acetate, as the source of ammonia, and an appropriate solvent, for example acetic acid or DMSO. The imidazole 4 may then be transformed into other imidazoles 5 by appropriate functional group interconversion procedures. Scheme I also illustrates the preparation of a protected  $\alpha$ -hydroxyketone 2a, by condensing the anion of 1 with an appropriately activated carbonyl derivative of a substituted benzamide, such as the N-methoxy-N-methylamide, to yield a protected  $\alpha$ -hydroxyketone. This adduct 2a may then be directly converted to the imidazole 5, using a combination of a copper (II) salt, such as copper (II) acetate, as an oxidising agent and ammonium acetate as a source of ammonia. The  $\alpha$ -hydroxyketone 2a may also be deprotected and then oxidised to give an  $\alpha$ -diketone 3, for instance using Swern oxidation.





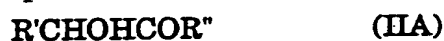
Scheme I

- 5 Scheme II illustrates the use of an  $\alpha$ -keto-oxime for preparing a compound of formula (I). A heterocyclic ketone 7 is prepared by adding the anion of 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone 7. The  $\alpha$ -keto-oxime 8 is then prepared from 7 using standard conditions, such as reaction with sodium nitrite, and this may then be reacted with a benzaldehyde to afford an N-hydroxyimidazole 9, a compound of formula (I) in which R<sub>2</sub> is hydroxy. This may be converted to 10, a further compound of formula (I) in which R<sub>2</sub> is hydrogen, by treating it with a deoxygenating agent such as phosphorus trichloride or a trialkyl phosphite, such as trimethyl or triethylphosphite. For compounds of formula (I) wherein R<sub>3</sub> is -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>-P(Z)-(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub>, the reagent OHC-(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>-P(Z)-(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> may be used instead of OHC-C<sub>6</sub>H<sub>4</sub>-X to make the appropriately substituted compound 9.
- 10
- 15



Scheme II

- 5 In a further process, a compound of formula (I) may be obtained by treating an  $\alpha$ -hydroxyketone compound of formula (IIA):



- wherein one of R' and R'' is R<sub>1</sub> and the other is R<sub>4</sub>, a suitably protected derivative thereof or the  $\alpha$ -hydroxy-oxime or  $\alpha$ -haloketone derivative thereof, with an oxidising agent capable of converting said compound into the corresponding  $\alpha$ -diketone, in the presence of an aldehyde of formula (III) or an equivalent thereof, and a source of ammonia. Suitable oxidising agents include, for example, an oxidising heavy metal salt, preferably an organic copper (II) salt, such as copper (II) acetate or copper (II) citrate. The reaction may be effected in a solvent such as acetic acid, under reflux conditions. Alternatively, a lower alkanol solvent, such as methanol or ethanol, may be used, preferably at a temperature in the region of from 30 to 100°C (see The Chemistry of Heterocyclic Compounds, Imidazole and its

derivatives, part I, ed. Weissberger, Interscience Publishers, Inc., New York, 1953, 38). This approach is also illustrated in Scheme I.

In a further process, a compound of formula (I) may be obtained by treating an amidine of formula (IV):



wherein  $\text{R}_2$  and  $\text{R}_3$  are as hereinbefore defined, or a salt thereof, with a reactive ester of an  $\alpha$ -hydroxyketone of formula (IIA) or the corresponding  $\alpha$ -haloketone, in an inert solvent such as a halogenated hydrocarbon solvent, for example chloroform, at a moderately elevated temperature and, if necessary, in the presence of a suitable condensation agent such as a base. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine of formula (IV) is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ*, by employing a two phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines of formula (IV) may be obtained by standard methods, see for instance, Garigipati R, Tetrahedron Letters, 190, 31, 1989.

In a further process, a compound of formula (I) may be obtained by treating an iminoether of formula (V):



wherein  $\text{R}_3$  is as hereinbefore defined and  $\text{R}$  is  $\text{C}_{1-10}$  alkyl, aryl or aryl  $\text{C}_{1-4}$  alkyl, with an  $\alpha$ -aminoketone of the formula (VI):



wherein one of  $\text{R}'$  and  $\text{R}''$  is  $\text{R}_1$  and the other is  $\text{R}_4$  in a suitable solvent.

In a further process, N-substituted compounds of formula (I) may be prepared by treating the anion of an amide of formula (VII):



wherein  $\text{R}_1$  and  $\text{R}_3$  are as hereinbefore defined and  $\text{R}_2$  is as hereinbefore defined other than hydrogen, with:

(a) a nitrile of the formula (VIII):



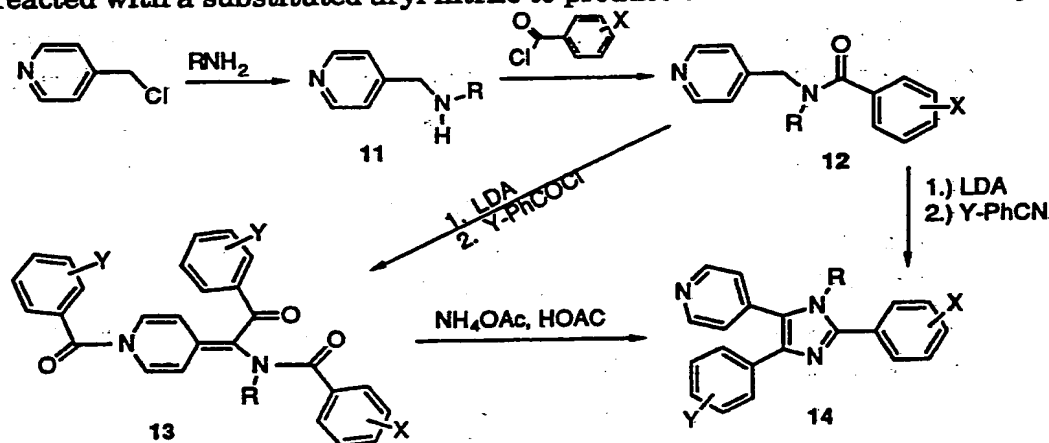
wherein  $\text{R}_4$  is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the formula (IX):



wherein  $R_4$  is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.

This approach permits the regiospecific preparation of compound of formula (I) substituted at the 1-position, as illustrated in Scheme III. A primary amine  $RNH_2$  is treated with 4-chloromethylpyridine to give 11 which is then converted to the amide 12 by standard techniques. Deprotonation of 12 with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound 13 which is then closed to an imidazole compound of formula (I), 14, by heating in acetic acid containing ammonium acetate. Alternatively, the anion of 12 may be reacted with a substituted aryl nitrile to produce the imidazole 14 directly.



Scheme III

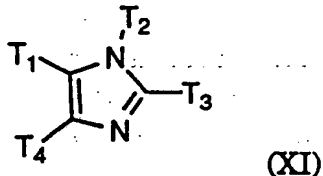
In a further process, compounds of formula (I) may be prepared by treating a compound of formula (X):



wherein  $R'$ ,  $R''$  and  $R_3$  are as hereinbefore defined and  $X_c$  is O or NH, with a source of ammonia, as hereinbefore described, under imidazole ring forming conditions or cyclising the corresponding Schiff's base, formed by treating the compound of formula (X) in which  $X_c$  is NH with an amine  $R_2NH_2$ , for instance thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, 28, 3381). Compounds of formula (X) may be obtained, for instance, by acylating the corresponding  $\alpha$ -keto-oxime ( $X_c$  is NH) or  $\alpha$ -hydroxyketone ( $X_c$  is O) with an

acyl halide of the formula  $R_3COHal$  wherein  $R_3$  is as hereinbefore defined, or the corresponding anhydride, under standard acylating conditions.

In a further process, compounds of formula (I) may be prepared by coupling a suitable derivative of a compound of formula (XI):



5 wherein:  $T_2$  is a nitrogen protecting group or  $R_2$ , other than hydrogen; and  $T_1$  is hydrogen,  $T_3$  is Q and  $T_4$  is  $R_4$ ;  $T_1$  is  $R_1$ ,  $T_3$  is hydrogen and  $T_4$  is  $R_4$ ; or  $T_1$  is  $R_1$ ,  $T_3$  is Q and  $T_4$  is hydrogen, in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and Q are as hereinbefore defined; with: (i) when  $T_1$  is hydrogen, a suitable derivative of  
10 the heteroaryl ring  $R_1H$ , under ring coupling conditions, to effect coupling of the heteroaryl ring  $R_1$  to the imidazole nucleus at position 5; (ii) when  $T_3$  is hydrogen, a suitable derivative of the aryl or heteroaryl ring QH, under ring coupling conditions, to effect coupling of the ring Q to the imidazole nucleus at position 2; or (iii) when  $T_4$  is hydrogen, a suitable derivative of the aryl  
15 ring  $R_4H$ , under ring coupling conditions, to effect coupling of the aryl ring  $R_4$  to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second  
20 component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of formula (XI), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of formula (XI)  
25 or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is herewith incorporated.

30 Suitable organomagnesium and organozinc derivatives of a compound of formula (XI) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (0) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, 22, 5319 (1981). Suitable  
35 such catalysts include *tetrakis*-(triphenylphosphine)palladium and

PdCl<sub>2</sub>[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl<sub>2</sub>(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen, J Org Chem, 1982, 47, 4319. Suitable reaction solvents include hexamethylphosphoramide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound of formula (XI) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

A trialkyltin derivative of the compound of formula (XI) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)palladium, by the method described in by Stille, J Amer Chem Soc, 1987, 109, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of formula (XI) with a lithiating agent, such as *s*-butyllithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of formula (XI) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of formula (XI) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis*-(triphenylphosphine)-palladium, under conditions similar to those described above.

Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of formula (XI), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or PdCl<sub>2</sub>[1,4-*bis*-(diphenylphosphino)-

butane] in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, 84, 439, 1965, Snieckus, V., Tetrahedron Lett., 29, 2135, 1988 and Terashimia, M., Chem. Pharm. Bull., 11, 4755, 1985).

5 Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al*, J Org Chem, 49, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

10 In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of formula (XI). Thus, in general, amino and sulfur substituents should be non-oxidised or protected and the N-1 nitrogen of a compound of formula (XI) be protected, if an NH compound is finally required. Nitro, 15 bromo, iodo and hydroxyl groups should preferably be avoided in compounds of formula (XI) in which T<sub>1</sub> is hydrogen.

Compounds of formula (XI) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of 20 formula (I). In particular, an  $\alpha$ -halo-ketone R<sub>4</sub>COCH<sub>2</sub>Hal (for compounds of formula (XI) in which T<sub>1</sub> is hydrogen) or R<sub>1</sub>COCH<sub>2</sub>Hal (for compounds of formula (XI) in which T<sub>4</sub> is hydrogen) may be reacted with an amidine of formula (IV) or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated 25 temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable  $\alpha$ -halo-ketones is described in WO 91/19497. For a compound of formula (XI) in which T<sub>3</sub> is hydrogen, an  $\alpha$ -diketone of formula (II) may be condensed with a formaldehyde or an equivalent thereof, in the presence of a source of 30 ammonia. Suitable bromo derivatives of the compound of formula (XI) may be obtained by brominating the corresponding compound of formula (XI) under standard brominating conditions, for instance bromine in a solvent such as dichloromethane or THF.

Compounds of formula (I) may also be prepared by a process which 35 comprises reacting a compound of formula (XI), wherein T<sub>1</sub> is hydrogen, with an N-acyl heteroaryl salt, according to the method disclosed in US patents 4,803,279, 4,719,218 and 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be

subjected to oxidative-deacylation conditions. The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of formula (XI) in the heteroaryl compound  $R_1H$  or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidising conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated in their entirety. Suitable oxidising systems include sulfur in an inert solvent or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

Once the imidazole nucleus has been established, further compounds of formula (I) which may be prepared by applying standard techniques for functional group interconversion, for instance:  $-C(O)NR_8R_9$  from  $-CO_2CH_3$  by heating with or without catalytic metal cyanide, e.g. NaCN, and  $HNR_8R_9$  in  $CH_3OH$ ;  $-OC(O)R_8$  from  $-OH$  with e.g.,  $ClC(O)R_8$  in pyridine;  $-NR_{10}-C(S)NR_8R_9$  from  $-NHR_{10}$  with an alkylisothiocyanate or thiocyanic acid;  $NR_6C(O)OR_6$  from  $-NHR_6$  with the alkyl chloroformate;  $-NR_{10}C(O)NR_8R_9$  from  $-NHR_{10}$  by treatment with an isocyanate, e.g.  $HN=C=O$  or  $R_{10}N=C=O$ ;  $-NR_{10}-C(O)R_8$  from  $-NHR_{10}$  by treatment with  $Cl-C(O)R_8$  in pyridine;  $-C(=NR_{10})NR_8R_9$  from  $-C(NR_8R_9)SR_8$  with  $H_3NR_8^+OAc^-$  by heating in alcohol;  $-C(NR_8R_9)SR_8$  from  $-C(S)NR_8R_9$  with  $R_6-I$  in an inert solvent, e.g. acetone;  $-C(S)NR_8R_9$  (where  $R_8$  or  $R_9$  is not hydrogen) from  $-C(S)NH_2$  with  $HNR_8R_9$ ,  $-C(=NCN)-NR_8R_9$  from  $-C(=NR_8R_9)-SR_8$  with  $NH_2CN$  by heating in anhydrous alcohol, alternatively from  $-C(=NH)-NR_8R_9$  by treatment with  $BrCN$  and  $NaOEt$  in  $EtOH$ ;  $-NR_{10}-C(=NCN)SR_8$  from  $-NHR_{10}$  by treatment with  $(R_8S)_2C=NCN$ ;  $-NR_{10}SO_2R_8$  from  $-NHR_{10}$  by treatment with  $ClSO_2R_8$  by heating in pyridine;  $-NR_{10}C(S)R_8$  from  $-NR_{10}C(O)R_8$  by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide];  $-NR_{10}SO_2CF_3$  from  $-NHR_6$  with triflic anhydride and base;  $-NR_{10}C(O)-C(O)-OR_8$  from  $-NHR_{10}$  with, e.g. methyloxalyl chloride and a base such as triethylamine;  $-NR_{10}C(O)-C(O)-NR_8R_9$  from  $-NR_{10}C(O)-C(O)-OR_8$  with  $HNR_8R_9$ ; and 1-( $NR_{10}$ )-2-imidazolyl from  $-C(=NH)NHR_{10}$  by heating with 2-chloroacetaldehyde in chloroform (wherein  $R_6$ ,  $R_8$ ,  $R_9$  and  $R_{10}$  are as hereinbefore defined).



Compounds of formula (I) in which R<sub>2</sub> is hydrogen may be readily converted into further compounds of formula (I) in which R<sub>2</sub> is other than hydrogen, for instance alkyl, by conventional procedures such as alkylation or acylation followed by reduction. Such methods are in general relatively inefficient as they lack regiospecificity and the desired N-1 product has to be separated from the mixture of N-1 and N-3 products, for instance by chromatography or fractional crystallisation.

Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>. Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

Pharmaceutically acid addition salts of compounds of formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

## 20 METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In particular, compounds of formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic  $\beta$  cells and Alzheimer's disease.

In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which

are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of formula (1). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but  
5 not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 Compounds of formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such  
15 viruses include, but are not limited to, the lentivirus infections such as equine infectious anaemia virus, caprine arthritis virus, visna virus, or the maedi virus, or the retroviruses, such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus.

The compounds of formula (I) may also be used topically in the  
20 treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with  
25 inflammation.

Compounds of formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8; NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an  
30 effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as,  
35 psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF,

and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of formula (I) are administered in an amount  
5 sufficient to inhibit cytokine, in particular IL-1, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-8 or  
10 TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-8 or TNF; or (iii) the presence of IL-1, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of formula (I) are inhibitors of  
15 cytokines, specifically IL-1, IL-8 and TNF is based upon the effects of the compounds of formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-8 or TNF)" refers to:

20 a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels  
25 of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo*  
30 levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be  
35 released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) and Tumor Necrosis Factor beta (TNF- $\beta$ ).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF- $\beta$  (also known as lymphotoxin) has close structural homology with TNF- $\alpha$  (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- $\alpha$  and TNF- $\beta$  are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation.

5 The compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound.

10 These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and

15 other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

25 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will

30 be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the

35 instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active  
5 ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for  
10 application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as  
15 glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-  
20 aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an  
25 alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as  
30 lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably  
35 including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of

bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

5       Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by  
10       conventional techniques. Compounds of formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

15       For all methods of use disclosed herein for the compounds of formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2  
20       to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the  
25       optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also  
30       be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

35       The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.



## Synthetic Examples

**Example 1 - 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole -** To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-N-

1-hydroxy-5-(4-pyridyl)imidazole (4.5 g, 13.2 mmol) [See Ex. 10 below] in  
5 DMF (50 mL) was added triethyl phosphite (3.4 mL, 20 mmol), and the  
resulting mixture was heated at 100 °C for 2 h. After cooling, the mixture  
was poured into H<sub>2</sub>O, and the solid which formed was collected by filtration,  
washed with H<sub>2</sub>O and dried *in vacuo* to afford the title compound (4.0 g,  
89%). Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/MeOH gave white solid with a mp of  
10 268-269 °C.

**Example 2 - 1-Methyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-pyridyl)-imidazole - (a) N-Methyl-N-(4-picolyl)amine-** To 4-picolyl chloride,

hydrochloride (10 g, 0.06 mol) was added methylamine (50 mL of 40%  
aqueous solution, 0.58 mol), and the resulting purple solution was stirred at  
15 rt for 30 min, then poured into H<sub>2</sub>O. The mixture was extracted with  
CH<sub>2</sub>Cl<sub>2</sub> (6x), and the combined organic extracts were evaporated. The  
residue was filtered under reduced pressure through a silica gel column,  
eluting with a solvent gradient of 0-10% MeOH/CHCl<sub>3</sub> to provide the title  
compound as a light yellow oil (4.8 g, 66%): <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.50 (dd,  
20 2H); 7.20 (dd, 2H); 3.70 (s, 2H); 2.40 (s, 3H); 1.70 (br, 1H).

**(b) 4-Methoxy-N-methyl-N-(4-picolyl)benzamide -** To a  
solution of N-methyl-N-(4-picolyl)amine (0.40 g, 3.3 mmol) and  
triethylamine (1.5 mL, 10.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added 4-  
methoxybenzoyl chloride (1.2 g, 7.3 mmol). The resulting mixture was  
25 stirred at rt for 15 min, and then partitioned between 2.5N NaOH and  
Et<sub>2</sub>O. The organic extract was washed with saturated aqueous NaCl and  
dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*, and the residue was  
purified by flash chromatography, eluting with a solvent gradient of 2-4%  
MeOH/CHCl<sub>3</sub>. The material that was isolated was triturated with Et<sub>2</sub>O to  
30 provide the title compound as a light yellow solid (0.18 g, 21%): <sup>1</sup>H NMR  
(CDCl<sub>3</sub>): δ 8.60 (d, 2H); 7.43 (br d, 2H); 7.20 (br s, 2H); 6.90 (br d, 2H); 4.66  
(br s, 2H); 3.80 (s, 3H); 3.00 (s, 3H).

**(c) 1-Methyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-pyridyl)-imidazole -** To a solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF  
35 at -78 °C was added n-butyllithium (0.38 mL of 2.5 M solution, 0.95 mmol).  
To the resulting mixture was added a solution of 4-methoxy-N-methyl-N-(4-  
picolyl)benzamide (0.16 g, 0.62 mmol) in THF. The resulting dark red  
solution was warmed to -40 °C and stirred for 15 min, at which time  
benzonitrile (0.13 mL, 1.2 mmol) was added. The mixture to warmed to rt

and stirred for 10 h. Aqueous  $\text{NH}_4\text{Cl}$  (0.5 mL) was added, and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 2-4%  $\text{MeOH}/\text{CHCl}_3$ . The material which was isolated was triturated with  $\text{Et}_2\text{O}$  and recrystallized from  $\text{EtOAc}$  to provide the title compound as an off-white solid (35 mg, 17%): mp 193-194 °C.

**Example 3 - 2-(4-Cyanophenyl)-1-methyl-4-phenyl-5(4-**

**pyridyl)imidazole - (a) 4-Cyano-N-methyl-N-(4-picolyl)benzamide -**

The title compound was prepared using the same procedure as described in Example 2, step (b) except using 4-cyanobenzoyl chloride:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.49 (dd, 2H); 7.86-7.04 (m, 6H); 4.70 and 4.43 (two br s, 2H); 3.08 and 2.89 (two br s, 3H).

(b) 4-Cyano-N-[N'- $\alpha$ -dibenzoyl-1,4-dihydropyridyl-methylenyl]-N-methylbenzamide - To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF at -78 °C was added n-butyllithium (6.7 mL of 2.5 M solution, 17 mmol). To the resulting mixture was added a solution of 4-cyano-N-methyl-N-(4-picolyl)benzamide (3.5 g, 14 mmol) in THF. The resulting dark purple solution was stirred at -78 °C for 10 min, at which time benzoyl chloride (4.1 mL, 35 mmol) was added. The mixture was warmed to room temperature over 30 min, then poured into aqueous  $\text{NH}_4\text{Cl}$ . The mixture was extracted with  $\text{Et}_2\text{O}$ , and the organic extract was evaporated under reduced pressure. The residue was triturated with  $\text{Et}_2\text{O}$  to provide an orange solid which was washed sparingly with acetone and copiously with  $\text{Et}_2\text{O}$ . The title compound was obtained as a bright yellow solid (1.6 g, 25%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.81-7.09 (m, 16H); 6.49 (m, 2H); 3.32 (s, 3H).

(c) 2-(4-Cyanophenyl)-1-methyl-4-phenyl-5(4-pyridyl)imidazole - To a solution of 4-cyano-N-[N'- $\alpha$ -dibenzoyl-1,4-dihydropyridylmethylenyl]-N-methylbenzamide (1.5 g, 3.3 mmol) in acetic acid (50 mL) was added ammonium acetate (1.5 g, 19.5 mmol). The resulting mixture was heated at reflux for 18 h, then allowed to cool and was concentrated. The residue was suspended in  $\text{CH}_2\text{Cl}_2$  and filtered. The filtrate was evaporated and the residue was triturated with MeOH to afford the title compound as a white crystalline solid (0.72 g, 64%): mp 176-177 °C.

**Example 4 - 2-(4-Aminomethylphenyl)-1-methyl-4-phenyl-5(4-pyridyl)imidazole -** To a solution of 2-(4-cyanophenyl)-1-methyl-4-phenyl-5(4-pyridyl)imidazole (0.20 g, 0.6 mmol) [See Ex. 3 above] in THF (10 mL) was added  $\text{LiAlH}_4$  (0.60 mL of 1.0 M solution in THF, 0.6 mmol), and the

resulting mixture was stirred at rt for 1 h. The mixture was then poured into 2.5 N NaOH and extracted with Et<sub>2</sub>O. The organic extract was evaporated, and the residue was purified by flash chromatography, eluting first with a solvent gradient of 0-10% MeOH/CHCl<sub>3</sub>, followed by 1:10:90

5 NH<sub>4</sub>OH/MeOH/CHCl<sub>3</sub>. Trituration with ether afforded the title compound as a white solid (66 mg, 32%): CIMS (NH<sub>3</sub>, *m/z*): 341 (M<sup>+</sup>+H).

**Example 5 - 4-[1-Methyl-4-phenyl-5(4-pyridyl)-imidazol-2-yl] benzoic acid, sodium salt** - A mixture of 2-(4-cyanophenyl)-1-methyl-4-phenyl-5(4-pyridyl)imidazole (0.10 g, 0.3 mmol) [See Ex. 3 above] in 6 N HCl (3 mL)

10 was heated at reflux for 24 h, then allowed to cool. The pH was adjusted to 7, and the solid which formed was collected by filtration and washed successively with H<sub>2</sub>O, acetone and Et<sub>2</sub>O to provide the title compound as a white solid (25 mg, 23%): CIMS (NH<sub>3</sub>, *m/z*): 356 (M<sup>+</sup>+H).

**Example 6 - 2-(4-Acetamidomethylphenyl)-1-methyl-4-phenyl-5-(4-pyridyl)imidazole** - To a solution of 2-(4-aminomethylphenyl)-1-methyl-4-phenyl-5-(4-pyridyl)imidazole (30 mg, 0.09 mmol) [See Ex. 4 above] in pyridine (3 mL) was added acetic anhydride (0.30 mL, 3.18 mmol). The resulting solution was stirred at rt for 30 min, then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 0-2% MeOH/CHCl<sub>3</sub>. The isolated material was trituated with Et<sub>2</sub>O to provide an off-white solid (10 mg, 28%) which was recrystallized from EtOAc to provide the title compound: mp 210-211 °C.

**Example 7 - Methyl-4-[1-methyl-4-phenyl-5-(4-pyridyl)-imidazol-2-yl] benzoate** - To a suspension of 4-[1-methyl-4-phenyl-5(4-pyridyl)-imidazol-2-yl] benzoic acid, sodium salt (20 mg, 0.06 mmol) [See Ex. 5 above] in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added triethylamine (24 mL, 0.17 mmol), followed by thionyl chloride (10 mL, 0.14 mmol). The reaction mixture was stirred at rt for 30 min, at which time MeOH (0.5 mL) was added. The mixture was stirred at rt for an additional 2 h and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 0-1% MeOH/CHCl<sub>3</sub> and recrystallized from EtOAc to afford the title compound as an off-white crystalline solid (1.6 mg, 8%): mp 208-209 °C.

**Example 8a - 4-(4-Fluorophenyl)-N-1-hydroxy-2-(4-hydroxyphenyl)-5-(4-pyridyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 4-hydroxybenzaldehyde.

**Example 8b - 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure

as described in Example 1, except using 4-(4-fluorophenyl)-N-1-hydroxy-2-(4-hydroxyphenyl)-5-(4-pyridyl)imidazole (see Ex.8a): mp 214-215 °C.

**Example 9 - 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzoic acid** - A solution containing 2-(4-cyanophenyl)-4-(4-fluoro-

5 phenyl)-5-(4-pyridyl)-1H-imidazole (9.6 g, 28 mmol) [See Ex. 1 above] in concentrated HCl (100 mL) was heated at reflux for 18 h. After cooling, the pH was adjusted to neutral by the addition of 50% aqueous NaOH. The solid which formed was collected by filtration and washed successively with H<sub>2</sub>O, acetone and Et<sub>2</sub>O. A portion of the solid (5 g) was dissolved in MeOH  
10 and filtered under reduced pressure through a pad of silica gel, eluting with a solvent gradient of 4-10 % MeOH/CHCl<sub>3</sub>, followed by 2:20:80 H<sub>2</sub>O/MeOH/CHCl<sub>3</sub>. The title compound was isolated as a yellow solid, which was recrystallized from MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1.2 g, 30% adjusted yield): mp 289-290 °C.

**Example 10 - 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-1-N-hydroxy-5-(4-**

15 **pyridyl)imidazole - (a) 4-Fluoro-N-methoxy-N-methylbenzamide**  
- To a mixture containing methoxymethylamine hydrochloride (44 g, 0.45 mol) and triethylamine (138 mL, 0.99 mol) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0 °C was added over 30 min, 4-fluorobenzoyl chloride (50 mL, 0.41 mol). The resulting mixture was allowed to warm to rt and stirring was continued for 30  
20 min, at which time the mixture was poured into H<sub>2</sub>O and extracted with Et<sub>2</sub>O. The organic extract was washed with saturated aqueous NaCl and dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* afforded the title compound (80 g, 100%), which was used without further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.72 (dd, 2H); 7.06 (apparent t, 2H); 3.52 (s, 3H); 3.43 (s, 3H).

25 **(b) 4-Fluoro-2-(4-pyridyl)acetophenone** - A solution of lithium diisopropylamide was prepared at -78 °C in the usual manner from diisopropylamine (21 mL, 0.15 mol) and n-butyllithium (54 mL of 2.5 M solution in hexanes, 0.135 mol), and to this was added at -78 °C, 4-picoline (10 g, 0.108 mol). After stirring an additional 15 min at -78 °C, 4-fluoro-N-methoxy-N-methylbenzamide (20 g, 0.109 mol) was added, and the mixture  
30 was allowed to slowly warm to rt. The reaction mixture was poured into saturated aqueous NaCl and extracted with 4:1 THF/CH<sub>2</sub>Cl<sub>2</sub>, and the organic extract was dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*, and to the oily brown residue was added Et<sub>2</sub>O. The title compound was obtained  
35 as a brown solid (16.8 g, 72%) which was recrystallized from Et<sub>2</sub>O/Hex: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.55 (d, 2H); 8.03 (dd, 2H); 7.16 (m, 4H); 4.24 (s, 2H).

**(c) 4-Fluoro-2-hydroxyimino-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure (US 3,940,486)

employed to prepare 2-hydroxyimino-2-(4-pyridyl)acetophenone, except using 4-fluoro-2-(4-pyridyl)acetophenone.

(d) **2-(4-Cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole** - The title compound was prepared using the same procedure (US 3,940,486) employed to prepare 2-(t-butyl)-4-(phenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole, except using 4-fluoro-2-hydroxyimino-2-(4-pyridyl)acetophenone and 4-cyanobenzaldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.27 (d, 2H); 7.94 (d, 2H); 7.72 (d, 2H); 7.35 (d, 2H); 7.30 (dd, 2H); 6.96 (t, 2H).

**Example 11 - 2-(4-Aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (2.5 g, 7.3 mmol) [See Ex. 1 above] in THF (50 mL) was added  $\text{LiAlH}_4$  (7.3 mL of 1 M solution in THF, 7.3 mmol), and the resulting mixture was heated at reflux for 2 h, at which time tlc analysis indicated that the reaction was incomplete. Additional  $\text{LiAlH}_4$  (4.0 mL, 4.0 mmol) was added and heating was continued for 30 min. The mixture was allowed to cool, then poured into 2.5 N NaOH and extracted with THF. The organic extract was washed with saturated aqueous NaCl and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 9:1  $\text{CHCl}_3/\text{MeOH}$ , followed by 90:10:1  $\text{CHCl}_3/\text{MeOH}/\text{NH}_3$ . The material that was isolated was triturated with  $\text{Et}_2\text{O}$  to afford the title compound (1.5 g, 60%): mp 214-215 °C.

**Example 12a - 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-quinolyl)imidazole - (a) 4-Fluoro-2-(4-quinolyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 4-methylquinoline:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.87 (d, 1H); 8.13 (m, 3H); 7.86 (d, 1H); 7.73 (apparent br t, 1H); 7.56 (apparent br t, 1H); 7.28 (d, 1H); 7.20 (t, 2H); 4.71 (s, 2H).

**(b) 4-Fluoro-2-hydroxyimino-2-(4-quinolyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 4-fluoro-2-(4-quinolyl)acetophenone:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  9.00 (d, 1H); 8.15 (m, 3H); 7.78 (m, 1H); 7.61 (m, 2H); 7.50 (d, 1H); 7.42 (t, 2H).

**(c) 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-quinolyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 4-fluoro-2-hydroxyimino-2-(4-quinolyl)acetophenone and 4-cyanobenzaldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.30 (d, 2H); 7.80 (d, 1H); 7.70 (two overlapping d, 3H); 7.46 (m, 2H); 7.36 (m, 1H); 7.11 (m, 2H); 7.01 (m, 1H); 6.75 (t, 2H).

**Example 12b - 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-quinolyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using 2-(4-cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-quinolyl)imidazole [see Ex. 12a]: mp 294-295 °C.

5 **Example 13 - 2-(3,5-Dibromo-4-hydroxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole - (a) 1-(4-fluorophenyl)-2-(4-pyridyl)-ethanediol** To a stirring solution of 2.0 g (11.2 mmol) 4-(t-butyldimethylsilyloxy)methyl pyridine in 8 ml of THF at -20° C was added 14.7 mmol of lithium di-iso-propyl amide in THF. Thirty minutes later 4-fluoro-  
10 benzaldehyde (1.66 g, 13.4 mmol) was added at which point the solution was allowed to warm slowly to rt. The reaction was quenched with NH<sub>4</sub>Cl and extracted with ether to afford the crude protected diol which following concentration was dissolved in THF and treated with 17 ml of a 1 molar solution of tetrabutylammonium fluoride in THF overnight. Standard  
15 aqueous workup afforded the crude diol which was further purified by column chromatography (hex/EtOAc) to yield 1.6 g (62%) of the titled material.

(b) 1-(4-fluorophenyl)-2-(4-pyridyl)ethanedione Oxidation of 1-(4-fluorophenyl)-2-(4-pyridyl)ethanediol according to the oxalyl chloride method of Swern [J. Org. Chem., 44, p 4148, 1979] gave the titled dione  
20 following extractive workup and recrystallization from hexanes m.p. 85-86.5°C.

(c) 2-(3,5-Dibromo-4-hydroxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole To a solution of 1-(4-fluorophenyl)-2-(4-pyridyl)ethanedione (0.25 g, 1.1 mmol) and 3,5-dibromo-4-hydroxy-  
25 benzaldehyde (0.37 g, 1.3 mmol) in glacial acetic acid (5 mL) was added ammonium acetate (0.50 g, 6.5 mmol), and the resulting mixture was heated at reflux for 18 h. After cooling, the mixture was poured into H<sub>2</sub>O, and the pH was adjusted to neutral by the addition of 2.5 N NaOH. The solid which formed was collected by filtration, washed with H<sub>2</sub>O, dried *in vacuo* and  
30 purified by flash chromatography, eluting with a solvent gradient of 2-4% MeOH/CHCl<sub>3</sub>. The title compound was obtained as a tan solid (15 mg, 3%): ESMS (*m/z*): 488 (M<sup>+</sup>+H).

**Example 14 - Ethyl 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)]-1H-imidazol-2-yl]-benzoate** - A solution of 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoic acid (30 mg, 0.08 mmol) See Ex. 9 above] in 20%  
35 ethanolic HCl (5 mL) was heated at reflux for 24 h, cooled to rt and neutralized with 50 % NaOH. The residue was collected and purified by flash chromatography eluting with a solvent gradient of 4-10% MeOH/CHCl<sub>3</sub>. Trituration with Et<sub>2</sub>O afforded the title compound as a

white solid (3.2 g 66%).  $^1\text{H}$  NMR ( $\text{CDCl}_3/\text{MeOH}-d_4$ ):  $\delta$  8.45 (d, 2H); 8.12 (m, 4H); 7.52 (m, 4H); 7.15 (t, 2H); 4.42 (q, 2H); 1.43 (t, 3H).

**Example 15 - 2-[3,5-Dimethyl-4-hydroxy(phenyl)]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 3,5-dimethyl-4-hydroxybenzaldehyde: ESMS ( $m/z$ ): 360 ( $\text{M}^++\text{H}$ ).

**Example 16 - 4-(4-Fluorophenyl)-2-(2-hydroxyphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using salicylaldehyde: ESMS ( $m/z$ ): 332 ( $\text{M}^++\text{H}$ ).

**Example 17 - 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-(methylthio)benzaldehyde: ESMS ( $m/z$ ): 362 ( $\text{M}^++\text{H}$ ).

**Example 18 - Methyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoate** - A mixture containing 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzoic acid, sodium salt (0.20 g, 0.5 mmol) [See Ex. 9 above] and concentrated HCl (10 drops) in MeOH (5 mL) was heated at reflux for 8 h. After cooling, the pH was adjusted to neutral by the addition of 2.5 N NaOH, and the solid which formed was collected by filtration, washed with  $\text{H}_2\text{O}$  and dried *in vacuo*. The title compound was obtained as a yellow solid (0.14 g, 76%) and was recrystallized from EtOAc/ $\text{CH}_2\text{Cl}_2$ :  $^1\text{H}$  NMR ( $\text{CDCl}_3/\text{MeOH}-d_4$ ):  $\delta$  8.36 (d, 2H); 8.03 (m, 4H); 7.60-7.30 (m, 4H); 7.07 (t, 2H); 3.84 (s, 3H).

**Example 19 - 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole** - To a solution of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole (3.7 g, 9.8 mmol) [See Ex. 20 below] in 1:10 3 N HCl/ $\text{H}_2\text{O}$  (88 mL) was added a solution of  $\text{KMnO}_4$  (1.5 g, 9.8 mmol) in  $\text{H}_2\text{O}$  (15 mL). After stirring at rt for 1 h, additional  $\text{KMnO}_4$  (0.15 g, 0.9 mmol) was added, and stirring was continued for 15 min. The mixture was then poured into saturated aqueous  $\text{Na}_2\text{SO}_3$  (200 mL), and the pH was adjusted to slightly acidic by the addition of 3 N HCl, then to neutral by the addition of 2.5 N NaOH. The solid which formed was collected by filtration, washed successively with  $\text{H}_2\text{O}$  and MeOH and recrystallized three times from MeOH to afford the title compound (0.63 g, 16%): mp 148-149 °C.

**Example 20 - 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole** - To a solution of 4-(4-fluorophenyl)-2-(4-

methylthiophenyl)-5-(4-pyridyl)-1H-imidazole (0.80 g, 2.2 mmol) [See Ex. 17 above] in glacial acetic acid (15 mL) was added a solution of  $K_2S_2O_8$  (0.72 g, 2.6 mmol) in  $H_2O$  (20 mL). Additional glacial acetic acid (15 mL) was added to ensure homogeneity, and the resulting solution was stirred at rt for 18 h. The mixture was then poured into  $H_2O$ , and the pH was adjusted to neutral by the addition of conc.  $NH_4OH$ . The solid which formed was collected by filtration to afford the title compound (0.65 g, 78%) as a tan solid, which was recrystallized from MeOH: mp 250-252 °C.

**Example 21 - N,N-Dimethyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide** - To dimethylamino(methyl)aluminum chloride (0.60 mL of 0.67 M solution in toluene, 0.40 mmol) was added a solution of methyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoate (50 mg, 0.13 mmol) [See Ex. 18 above] in 1,2-dichloroethane (5 mL). The resulting mixture was heated at reflux for 4 h, then allowed to cool and was poured into 2.5 N NaOH. The mixture was extracted with EtOAc, and the organic extract was washed with saturated aqueous NaCl and dried ( $MgSO_4$ ). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with a solvent gradient of 2-4% MeOH/ $CHCl_3$  to afford the title compound (25 mg, 50%) as a white solid: CIMS ( $NH_3$ ,  $m/z$ ): 387 ( $M^+ + H$ ).

**Example 22 - 2-[(4-N,N-Dimethyl)aminomethylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 11, except using N,N-dimethyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide: CIMS ( $NH_3$ ,  $m/z$ ): 373 ( $M^+ + H$ ).

**Example 23 - 2-[4-(Dimethylamino)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-(N,N-dimethylamino)benzaldehyde: ESMS ( $m/z$ ): 359 ( $M^+ + H$ ).

**Example 24 - 4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using benzaldehyde: ESMS ( $m/z$ ): 316 ( $M^+ + H$ ).

**Example 25 - 2-[4-(3-Dimethylaminopropoxy)phenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-(3-dimethylamino-propoxy)benzaldehyde: ESMS ( $m/z$ ): 417 ( $M^+ + H$ ).

**Example 26 - 4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as



described in Example 13, except using 4-nitrobenzaldehyde: ESMS (*m/z*): 359 (*M*<sup>+</sup>+H).

**Example 27 - N,N-Dimethyl-4-[2-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzoyl-oxyacetamide - (a) Methyl benzylglycolate -**

5 To a solution containing methyl glycolate (2.5 mL, 32 mmol) and trifluoromethyl-sulfonic acid (150 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added benzyl 2,2,2-trichloro-acetimidate (7.0 mL, 37 mmol). After stirring for several min, the mixture was poured into aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The organic extract was washed with saturated aqueous NaCl, dried  
10 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 9-17% EtOAc/Hex to afford the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.34 (m, 5H); 4.62 (s, 2H); 4.11 (s, 2H); 3.78 (s, 3H).

(b) Benzyl-N,N-dimethylglycolamide - To dimethyl-  
15 amino(methyl)aluminum chloride [prepared from dimethylamine hydrochloride (3.4 g, 42 mmol) and trimethyl aluminum (21 mL of 2 M solution, 42 mmol)] in toluene (40 mL) was added methyl benzylglycolate (3.0 g, 17 mmol). After stirring at rt for 1.5 h, the mixture was poured into 3 N HCl and extracted with Et<sub>2</sub>O. The organic extract was washed with  
20 saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 9-50% EtOAc/Hex. The title compound was obtained as a colorless oil (1.2 g, 37%): <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.4-7.1 (m, 5H); 4.61 (s, 2H); 4.18 (s, 2H); 2.98 (s, 3H); 2.95 (s, 3H).

25 (c) N,N-Dimethylglycolamide - To a solution of benzyl-N,N-dimethylglycolamide (0.28 g, 1.5 mmol) in MeOH (5 mL) was added 10% palladium on activated carbon (0.15 g), and the resulting mixture was stirred under an atmosphere of H<sub>2</sub>. After 1 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced  
30 pressure to afford the title compound which was used without further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.13 (s, 2H); 3.01 (s, 3H); 2.89 (s, 3H).

(d) N,N-Dimethyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoyl-oxyacetamide - To a solution of 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzoic acid (0.15 g, 0.42 mmol)  
35 [See Ex. 9 above] in DMF (10 mL) was added carbonyldiimidazole (0.34 g, 2.1 mmol). After stirring for 18 h at rt, N,N-dimethylglycolamide (0.43 g, 4.2 mmol) was added and stirring was continued for an additional 3h at rt. The reaction mixture was poured into H<sub>2</sub>O, extracted with EtOAc and evaporated. The residue was purified by flash chromatography eluting with

a solvent gradient of 2% MeOH/CHCl<sub>3</sub> to afford the title compound: CIMS (NH<sub>3</sub>, *m/z*): 445 (M<sup>+</sup>+H).

**Example 28 - 2-(4-Aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - A mixture containing 4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-

- 5 pyridyl)-1H-imidazole (2.0 g, 5.6 mmol) [See Ex. 26 above] and 10% palladium on activated carbon (0.4 g) was stirred under an atmosphere of H<sub>2</sub> for 4 h, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with a solvent gradient of 1-10% MeOH/CHCl<sub>3</sub>.  
10 The title compound was obtained as a light orange solid (0.50 g, 27%): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.40 (d, 2H); 7.73 (d, 2H); 7.57 (m, 2H); 7.35 (m, 4H); 6.62 (t, 2H).

**Example 29 - 4-(4-Fluorophenyl)-2-(4-methanesulfonamidophenyl)-5-**

- 15 (4-pyridyl)-1H-imidazole - To a suspension of 2-(4-aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (80 mg, 0.24 mmol) [See Ex. 28 above] and triethylamine (0.12 mL, 0.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added methanesulfonyl chloride (55 mL, 0.72 mmol). After stirring at rt for 1h, the mixture was poured into aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic extract was washed with saturated aqueous NaCl, dried  
20 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 2-10% MeOH/CHCl<sub>3</sub> to afford the title compound as a tan solid (35 mg, 36%): ESMS (*m/z*): 409 (M<sup>+</sup>+H).

**Example 30 - 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-**

- 25 yl]phenyl-sulfonamide - (a) Ethyl 4-sulfonamidobenzoate - A solution of 4-carboxybenzenesulfonamide (5.0 g, 0.025 mol) in 20% ethanolic HCl (20 mL) was heated at reflux for 18 h, then allowed to cool and was concentrated under reduced pressure to afford the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.20 (apparent d, 2H); 8.00 (apparent d, 2H); 4.88 (br s, 2H); 4.43  
30 (q, 2H); 1.43 (t, 3H).

(b) N-Methoxy-N-methyl-4-sulfonamidobenzamide - To a solution of methoxymethylamino(methyl)aluminum chloride [prepared from methoxymethylamine hydrochloride (4.8 g, 50 mmol) and trimethyl aluminum (25 mL of 2 M solution, 50 mmol)] in toluene (50 mL) at 0 °C was  
35 added ethyl 4-sulfonamidobenzoate (3.8 g, 17 mmol). The mixture was allowed to warm to rt and stir for 3 h, then was poured into a slurry of silica gel (50 g) in CHCl<sub>3</sub> (200 mL). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was poured into H<sub>2</sub>O,

and the solid which formed was collected by filtration, washed with H<sub>2</sub>O and dried *in vacuo* to afford the title compound (1.7 g, 42%): <sup>1</sup>H NMR (CDCl<sub>3</sub>/MeOH-d<sub>4</sub>): δ 7.86 (d, 2H); 7.66 (d, 2H); 3.43 (s, 3H); 3.29 (s, 3H).

- (c) **4-Formylbenzenesulfonamide** - To a solution of N-methoxy-N-methyl-4-sulfonamidobenzamide (1.0 g, 4.1 mmol) in THF (25 mL) at -78 °C was added LiAlH<sub>4</sub> (6.1 mL of 1 M solution in THF, 6.1 mmol). After stirring at -78 °C for 30 min, the mixture was poured into a slurry of silica gel (50 g) in CHCl<sub>3</sub> (200 mL). The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 2-10% MeOH/CHCl<sub>3</sub>. The title compound was obtained as a white solid (0.12 g, 16%): <sup>1</sup>H NMR (CDCl<sub>3</sub>/MeOH-d<sub>4</sub>): δ 10.3 (s, 1H); 8.02 (d, 2H); 7.95 (d, 2H).

- (d) **4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]sulfonamide** The title compound was prepared using the same procedure as described in Example 13, except using 4-formylbenzenesulfonamide: ESMS (*m/z*): 395 (M<sup>+</sup>+H).
- Example 31 - N'-Cyano-N-4-[4-(fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzylguanidine** - To a suspension of 2-(4-aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (0.10 g, 0.29 mmol) [See Ex. 11 above] in CH<sub>3</sub>CN was added diphenyl cyanocarbonimidate (83 mg, 0.35 mmol). After stirring at rt for 18 h, the solid which formed was collected by filtration and washed with CH<sub>3</sub>CN. The solid was dissolved in MeOH saturated with NH<sub>3</sub> and stirred for 72 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with a solvent gradient of 4-10% MeOH/CHCl<sub>3</sub>. The title compound was isolated as a pale yellow solid (22 mg, 18%): mp 280-281 °C.

- Example 32 - 2-[4-(Methanesulfonamido)methylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 29, except using 2-(4-aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 11 above]: ESMS (*m/z*): 423 (M<sup>+</sup>+H).

- Example 33 - 4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)-1H-imidazole** - (a) **1-Cyano-1-(4-pyridyl)methyl 4-methoxybenzoate** - The title compound was prepared using the same procedure Lantos, I. et al. (*J. Med. Chem.* 1984, 27, 72-75) employed to prepare 1-cyano-1-(4-pyridyl)-methyl benzoate, except using 4-methoxybenzoyl chloride: <sup>1</sup>H NMR

(CDCl<sub>3</sub>):  $\delta$  8.81 (d, 2H); 8.10 (d, 2H); 7.57 (d, 2H); 7.01 (d, 2H); 6.74 (s, 1H); 3.93 (s, 3H).

(b) **1-(4-Fluorophenyl)-2-(4-pyridyl)-2-oxoethyl 4-methoxybenzoate and 2-(4-fluorophenyl)-1-(4-pyridyl)-2-oxoethyl 4-**

5 **methoxybenzoate** - The title compounds were prepared using the same procedure Lantos et al. (J. Med. Chem. 1984, 27, 72-75) used to prepare 1-(4-Fluorophenyl)-2-(4-pyridyl)-2-oxoethyl benzoate and 2-(4-fluorophenyl)-1-(4-pyridyl)-2-oxoethyl benzoate, except using 1-Cyano-1-(4-pyridyl)methyl 4-methoxybenzoate: <sup>1</sup>H NMR (faster eluting isomer, CDCl<sub>3</sub>):  $\delta$  8.78 (d, 2H); 8.03 (br d, 2H); 7.73 (d, 2H); 7.53 (dd, 2H); 7.10 (apparent t, 2H); 6.93 (overlapping s and d, 3H); 3.85 (s, 3H); <sup>1</sup>H NMR (slower eluting isomer, CDCl<sub>3</sub>):  $\delta$  8.66 (d, 2H); 8.04 (m, 4H); 7.46 (d, 2H); 7.15 (apparent t, 2H); 6.95 (overlapping s and d, 3H); 3.87 (s, 3H).

(c) **4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)-1H-imidazole** - To a solution containing a mixture of 1-(4-fluorophenyl)-2-(4-pyridyl)-2-oxoethyl 4-methoxybenzoate and 2-(4-fluorophenyl)-1-(4-pyridyl)-2-oxoethyl 4-methoxybenzoate (0.35 g, 0.96 mmol) in glacial acetic acid (7.5 mL) was added ammonium acetate (0.35 g, 4.5 mmol). The resulting mixture was heated at reflux for 18 h, then allowed to cool. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with a solvent gradient of 33-60% EtOAc/Hex. The material which was isolated was recrystallized from MeOH/CH<sub>2</sub>Cl<sub>2</sub> to provide the title compound (65 mg, 20%) as an off-white solid: mp 264-265 °C.

25 **Example 34 - 2-(4-Amino-3-iodophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - To a solution of 2-(4-aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (50 mg, 0.15 mmol) [See Ex. 28 above] in glacial acetic acid (5 mL) was added a solution of ICl (24 mg, 0.15 mmol) in glacial acetic acid (1.5 mL). The resulting mixture was stirred at rt for 1 h, then poured into saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>. The pH was adjusted to neutral by the addition of 2.5 N NaOH and extracted with EtOAc. The organic extract was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with a solvent gradient of 2-10% MeOH/CHCl<sub>3</sub>. The material that was isolated was recrystallized from Et<sub>2</sub>O/Hex to afford the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.42 (d, 2H); 8.18 (d, 1H); 7.68 (dd, 2H); 7.42 (m, 4H); 7.09 (t, 2H); 6.77 (d, 1H).

**Example 35 - N-Benzyl-N-methyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide** - The title compound was prepared using the same procedure as described in Example 21, except using benzylmethylaminodimethyl aluminium and methyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoate [See Ex. 18 above]: mp 233-234 °C.

**Example 36 - 2-[4-(N-Benzyl-N-methyl)aminomethylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 11, except using N-benzyl-N-methyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide [See Ex. 35 above]: ESMS (*m/z*): 449 (*M*<sup>+</sup>+H).

**Example 37a - 4-(4-Fluorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-quinolyl)imidazole - (a) 4-Fluoro-2-(4-quinolyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 4-methylquinoline: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.87 (d, 1H); 8.10 (m, 3H); 7.88 (d, 1H); 7.74 (br t, 1H); 7.57 (br t, 1H); 7.20 (m, 3H); 4.73 (s, 2H).

**(b) 4-Fluoro-2-hydroxyimino-2-(4-quinolyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 4-fluoro-2-(4-quinolyl)acetophenone.

**(c) 4-(4-Fluorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-quinolyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 4-fluoro-2-hydroxyimino-2-(4-quinolyl)acetophenone and 4-(methylthio)benzaldehyde: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03 (m, 1H); 7.80 (br d, 2H); 7.52 (d, 1H); 7.40-7.10 (m, 5H); 6.81 (br m, 3H); 6.61 (apparent t, 2H), 2.48 (s, 3H).

**Example 37b - 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-quinolyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using 4-(4-fluorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-quinolyl)imidazole: ESMS (*m/z*): 412 (*M*<sup>+</sup>+H).

**Example 38 - 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-quinolyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20, except using 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-5-(4-quinolyl)-1H-imidazole: ESMS (*m/z*): 428 (*M*<sup>+</sup>+H).

**Example 39 - 4-(3-Chlorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20, except using 4-(3-chlorophenyl)-2-(4-

methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 40 below]: ESMS ( $m/z$ ): 394 ( $M^+ + H$ ).

**Example 40a - 4-(3-Chlorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole - (a) 3-Chloro-N-methoxy-N-**

- 5 **methylbenzamide** - The title compound was prepared using the same procedure as described in Example 10 (a) except using 3-chlorobenzoyl chloride:  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.69 (br s, 1H); 7.58 (br d, 1H); 7.42 (br d, 1H); 7.31 (dd, 1H); 3.55 (s, 3H); 3.34 (s, 3H).

- 10 **(b) 3-Chloro-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 4-picoline and 3-chloro-N-methoxy-N-methylbenzamide:  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.60 (d, 2H); 8.00 (br s, 1H); 7.89 (br d, 1H); 7.60 (br d, 1H); 7.45 (t, 1H); 7.21 (d, 2H); 4.27 (s, 2H).

- 15 **(c) 3-Chloro-2-hydroxyimino-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 3-chloro-2-(4-pyridyl)acetophenone.

- 20 **(d) 4-(3-Chlorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 3-chloro-2-hydroxyimino-2-(4-pyridyl)acetophenone and 4-methylthiobenzaldehyde:  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.04 (d, 2H); 7.70 (d, 2H); 7.21-6.91 (m, 8H); 2.47 (s, 3H).

- 25 **Example 40b 4-(3-Chlorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using 4-(3-chlorophenyl)-N-1-hydroxy-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole: ESMS ( $m/z$ ): 378 ( $M^+ + H$ ).

- 30 **Example 41 - 4-(4-Fluorophenyl)-2-(4-formamidomethylphenyl)-5-(4-pyridyl)-1H-imidazole** - Formic acid (10 ml) was added to acetic anhydride (20 mL) and the mixture was heated to 50 °C for 15 min. 2-(4-Aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole (0.25 g, 0.73 mmol) [See Ex. 11] was added and the reaction mixture was heated to 50 °C for 2 h. The solvent was evaporated and the residue was purified by flash chromatography, eluting with a solvent gradient of 4-10% MeOH/ $CHCl_3$ . The title compound was isolated as a tan solid (0.15 g, 55%): ESMS ( $m/z$ ): 373 ( $M^+ + H$ ).

- 35 **Example 42 - 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzohydroxamic acid** - To a solution of O-benzyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzohydroxamic acid (0.10 g, 0.22 mmol) [See Ex. 43 below] in ethanol (10 mL) was added 10 % palladium on carbon. After stirring under an atmosphere of  $H_2$  for 18 h, the reaction mixture was filtered through

celite and the solids were washed with ethanol. The combined filtrates were evaporated and the residue was recrystallized from 2-propanol to afford the title compound (0.040 g, 50%): ESMS ( $m/z$ ): 375 ( $M^++H$ ).

- Example 43 - O-Benzyl-4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzohydroxamic acid** - To a stirred suspension of O-benzyl-hydroxylamine hydrochloride (1.2 g, 7.8 mmol) in toluene (20 mL) at 0 °C was added trimethylaluminum (2.0 M in toluene, 3.9 mL, 7.8 mmol). The reaction mixture was warmed to rt and stirring was continued at this temperature for 1 h. Ethyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl] benzoate (1.0 g, 2.6 mmol) [See Ex. 14 above] was added and the reaction mixture was heated at reflux for 3 h. After cooling, the reaction was poured into 10% MeOH/ $CHCl_3$  containing silica gel. The solids were removed by filtration and washed with 10 % MeOH/ $CHCl_3$ . The combined washings were evaporated and the residue was purified by flash chromatography eluting with a solvent gradient of 1-10 % MeOH/ $CHCl_3$ . Trituration with ether afforded the title compound as a white solid (0.25 g, 21%):  $^1H$  NMR ( $CDCl_3$ / MeOH- $d_4$ ):  $\delta$  8.16 (d, 2H); 7.77 (d, 2H); 7.53 (d, 2H); 7.23 (m, 5H); 7.10 (m, 4H); 6.88 (t, 2H).

- Example 44 - 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide oxime** - To a mixture of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (3.0 g, 8.7 mmol) [See Ex. 1 above] and  $K_2CO_3$  (2.4 g, 17 mmol) in EtOH (120 mL) and  $H_2O$  (6 mL) was added hydroxylamine hydrochloride (1.2 g, 17 mmol). After heating at reflux for 24 h, the reaction mixture was poured into  $H_2O$ . The precipitate was collected, washed with  $H_2O$  and air-dried. The crude product was dissolved in acetone, silica gel was added and the solvent was evaporated. The impregnated silica gel was added to the top of a flash column and the column was eluted with a solvent gradient of 2-10 % MeOH/ $CHCl_3$  to afford the title compound as a white solid (3.0 g, 91 %): ESMS ( $m/z$ ): 374 ( $M^++H$ ).

- Example 45 - N'-Methyl-N'-cyano-N-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzylguanidine** - To a suspension of 2-(4-aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (2.5 g, 7.3 mmol) [See Ex. 11 above] in  $CH_3CN$  (250 mL) was added diphenyl cyanocarbonimidate (8.8 g, 7.3 mmol). After stirring at rt for 18 h, the solid which formed was collected by filtration and washed with  $CH_3CN$  (2.1 g, 59%). Without further purification, this material was added to methanol (100 mL) saturated with methylamine. The flask was stoppered and the reaction was stirred for 18 h at rt. The solvent and excess methylamine were evaporated and the residue was triturated with ether to give a brown solid which was further purified by flash chromatography eluting with a solvent gradient of 4-

10% MeOH/CHCl<sub>3</sub> to afford the title compound as a tan solid (0.33 g, 78%):  
CIMS (NH<sub>3</sub>, *m/z*): 426 (M<sup>+</sup>+H).

**Example 46a - N-1-Hydroxy-4-(3-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole - (a) 3-Methoxy-N-methoxy-N-methylbenzamide** - The title compound was prepared using the same procedure as described in Example 10, step (a) except using *m*-anisoyl chloride: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.27 (m, 3H); 7.01 (m, 1H); 3.82 (s, 3H); 3.57 (s, 3H); 3.36 (s, 3H).

**(b) 3-Methoxy-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 3-methoxy-N-methoxy-N-methylbenzamide: ESMS (*m/z*): 228.2 (M<sup>+</sup>+H).

**(c) 2-Hydroxyimino-3-methoxy-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 3-methoxy-2-(4-pyridyl)acetophenone.

**(d) N-1-Hydroxy-4-(3-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 2-hydroxyimino-3-methoxy-2-(4-pyridyl)acetophenone and 4-(methylthio)benzaldehyde: ESMS(*m/z*): 390 (M<sup>+</sup>+H).

**Example 46b - 4-(3-Methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using N-1-hydroxy-4-(3-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole: mp 215.0-216.0 °C.

**Example 47 - 4-(3-Methoxyphenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 38, except using 4-(3-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Example 46 above]: mp 167-168.5 °C.

**Example 48 - Morpholino-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide** - The title compound was prepared using the same procedure as described in Example 21 except using dimethylamino-

(morpholino)aluminum chloride and ethyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzoate [See Ex. 14 above]: ESMS (*m/z*): 429 (M<sup>+</sup>+H).

**Example 49 - 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-(4-fluorophenyl)-1-hydroxy-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)-imidazole [See Ex. 66 below]: ESMS (*m/z*): 376.2 (M<sup>+</sup>+H).



- Example 50 - 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylsulfinylphenyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20 except using 4-(4-fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)-1H-imidazole [See
- 5 **Ex. 49 above]**: ESMS ( $m/z$ ): 392.2 ( $M^+ + H$ ).
- Example 51a - 4-(4-Fluorophenyl)-N-1-hydroxy-5-(4-pyrimidinyl)-imidazole - (a) 4-Fluoro-2-(4-pyrimidinyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 4-methylpyrimidine.
- 10 **(b) 4-Fluoro-2-hydroxyimino-2-(4-pyrimidinyl)acetophenone** - The title compound was prepared using the same procedure described in Example 10, step (c) except using 4-fluoro-2-(4-pyrimidinyl)acetophenone.
- (c) 4-(4-Fluorophenyl)-N-1-hydroxy-5-(4-pyrimidinyl)imidazole** - The title compound was prepared using the same procedure described in
- 15 **Example 10, step (d) except using 4-fluorophenyl-2-hydroxyimino-2-(4-pyrimidinyl)acetophenone**.
- Example 51b - 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyrimidinyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using 4-(4-fluorophenyl)-N-
- 20 **1-hydroxy-5-(4-pyrimidinyl)imidazole**: CIMS ( $NH_3$ ,  $m/z$ ): 363 ( $M^+ + H$ ).
- Example 52 - 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyrimidinyl)-1H-imidazole** - The title compound was prepared using the same procedure described in Example 20, except using 4-(4-fluorophenyl)-2-(4-methylthio)phenyl)-5-(4-pyrimidinyl)-1H-imidazole: CIMS ( $NH_3$ ,  $m/z$ ): 379
- 25 ( $M^+ + H$ ).
- Example 53 - 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyrimidinyl)-1H-imidazole** - To a solution of 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyrimidinyl)-1H-imidazole (0.10 g, 0.28 mmol) [See Ex.
- 30 **51 above]** was added 3-chloroperbenzoic acid (50%, 0.15 g, 0.42 mmol). After stirring at rt for 72 h, the solvent was evaporated and the residue was partitioned between EtOAc and 2.5 N NaOH. The organic phase was washed with brine, dried ( $MgSO_4$ ) and evaporated. The residue was triturated with EtOAc to afford the title compound as a white solid (0.50 g, 46%). CIMS ( $NH_3$ ,  $m/z$ ): 395 ( $M^+ + H$ ).
- 35 **Example 54 - 4-(4-Fluorophenyl)-2-(4-Morpholinomethylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 11 except using morpholino-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide: mp 242-243 °C.

**Example 55 - 4-(4-Fluorophenyl)-2-(4-hydroxymethyl)-5-(4-pyridyl)-1H-imidazole** - To a suspension of ethyl 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl] benzoate (1.0 g, 2.6 mmol) [See Ex. 14 above] in THF (25 mL) was added LiAlH<sub>4</sub> (1 M in THF, 7.8 mL, 7.8 mmol). After stirring at rt for 0.5 h, the reaction mixture was poured into 2.5 N NaOH and extracted three times with 2:1 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated to afford the title compound as a white solid (0.50 g, 54%).

**Example 56 - 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-benzaldehyde** - To a suspension of 4-(4-fluorophenyl)-2-(4-hydroxymethyl)-5-(4-pyridyl)-1H-imidazole (0.40 g, 1.2 mmol) [See Ex. 55 above] in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added pyridinium chlorochromate (0.30 g, 1.4 mmol) at rt. The reaction mixture was stirred at this temperature for 2 h, filtered through a pad of silica gel eluting with 2% MeOH/CHCl<sub>3</sub> and the filtrate evaporated. The residue was purified by flash chromatography eluting with 4% MeOH/CHCl<sub>3</sub> followed by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/MeOH to afford the title compound as a white solid (0.30 g, 7.3%).

**Example 57 - 4-(2-Methoxyphenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20 except using 4-(2-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 58 below]: CIMS (NH<sub>3</sub>, *m/z*): 390 (M<sup>+</sup>+H).

**Example 58a - N-1-Hydroxy-4-(2-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole** - (a) **2-Methoxy-N-methoxy-N-methylbenzamide** - The title compound was prepared using the same procedure as described in Example 10, step (a) except using *o*-anisoyl chloride: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.36 (m, 3H); 6.98 (dd, 1H); 3.84 (s, 3H); 3.56 (br s, 3H); 3.32 (br s, 3H).

(b) **2-Methoxy-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 2-methoxy-N-methoxy-N-methylbenzamide.

(c) **2-Hydroxyimino-2-methoxy-2-(4-pyridyl)acetophenone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 2-methoxy-2-(4-pyridyl)acetophenone.

(d) **N-1-Hydroxy-4-(2-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 2-hydroxyimino-2-methoxy-2-(4-pyridyl)acetophenone and 4-(methylthio)benzaldehyde: ESMS (*m/z*): 390.0 (M<sup>+</sup>+H).

**Example 58b - 4-(2-Methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using N-1-hydroxy-4-(2-methoxyphenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole: CIMS (NH<sub>3</sub>, *m/z*): 374.2 (M<sup>+</sup>+H).

**Example 59 - 3-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl-5-methyl-4,5-dihydro-1,2,4-oxadiazole** - A solution of 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide oxime (0.50 g, 1.3 mmol) [See Ex. 44 above] and acetaldehyde (25 mL) in ethanol (100 mL) and H<sub>2</sub>O (100 mL) was stirred at rt for seven days. The solvent was evaporated and the residue was purified by flash chromatography eluting with a solvent gradient of 2-4% CHCl<sub>3</sub>/MeOH. Recrystallization from EtOAc afforded the title compound as a yellow solid (0.11 g, 21%): CIMS (NH<sub>3</sub>, *m/z*): 400 (M<sup>+</sup>+H).

**Example 60 - 3-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl-5-methyl-1,2,4-oxadiazole** - To a solution of 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide oxime (0.10 g, 0.27 mmol) [See Ex. 44 above] in pyridine (10 mL) was added acetic anhydride (1.0 mL) at rt. After stirring at this temperature for 18 h, the reaction mixture was poured into H<sub>2</sub>O, and the precipitate collected, washed with H<sub>2</sub>O and dried *in vacuo*. Without further purification, the crude o-acylamidoxime was dissolved in acetic acid (5 mL) and heated at reflux for 3 h. The solvent was evaporated, H<sub>2</sub>O was added and the mixture was neutralized with aqueous NaHCO<sub>3</sub>. The precipitate was collected, washed with H<sub>2</sub>O, air-dried and purified by flash chromatography eluting with 4% MeOH/CHCl<sub>3</sub>. Trituration with ether afforded the title compound as a white solid (0.030 g, 28%): CIMS (NH<sub>3</sub>, *m/z*): 398 (M<sup>+</sup>+H).

**Example 61 - 4-(3-Aminophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - A solution of 0.161 g (0.41 mmol) of 2-(4-methylthiophenyl)-4-(3-nitrophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 62 below] in 3.4 mL of HOAc-H<sub>2</sub>O (1:1) was treated with 1.81 mL (2.87 mmol) of 20% aqueous titanium (III) chloride in one single portion. The mixture was stirred at rt for 20 min, then made basic with 10% NaOH. The aqueous mixture was extracted with 95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The organic extracts were washed with H<sub>2</sub>O and saturated NaCl. Evaporation of solvent *in vacuo* afforded a yellow solid which was filtered through a plug of silica gel, eluting with 90:10 CHCl<sub>3</sub>/MeOH. The title compound was isolated as a pale yellow solid (0.129 g, 78%): CIMS (NH<sub>3</sub>, *m/z*): 359.1 (M<sup>+</sup>+H).

**Example 62a - N-1-Hydroxy-2-(4-methylthiophenyl)-4-(3-nitrophenyl)-5-(4-pyridyl)imidazole** - (a) 1-(3-Nitrophenyl)-2-(4-pyridyl)ethanol - The

title compound was prepared using the same procedure as described in Example 10, step (b) except using 3-nitrobenzaldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.41 (d, 2H); 8.23 (s, 1H); 8.15 (d, 1H); 7.67 (d, 1H); 7.54 (t, 1H); 7.19 (d, 2H); 5.05 (t, 1H); 4.41 (s, 2H).

- 5       **(b) 1-(3-Nitrophenyl)-2-(4-pyridyl)acetophenone** - To a solution of 1.0 mL (14.3 mmol) of DMSO in 55 mL of dry  $\text{CH}_2\text{Cl}_2$  was added 1.82 mL (12.9 mmol) of trifluoroacetic anhydride at  $-78^\circ\text{C}$ . The mixture was stirred for 30 min, then a solution of 1-(3-nitrophenyl)-2-(4-pyridyl)ethanol (1.09 g, 4.46 mmol) in DMSO/ $\text{CH}_2\text{Cl}_2$  (3/11 mL) was added dropwise. The mixture was  
10 stirred at  $-78^\circ\text{C}$  for 2 h, then 4.1 mL (29.4 mmol) of triethylamine was added dropwise. The ice bath was removed and the mixture was warmed to room temperature. The mixture was poured into saturated  $\text{NH}_4\text{Cl}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic extracts were washed with saturated  $\text{NH}_4\text{Cl}$  and saturated NaCl, then dried over  $\text{MgSO}_4$ . Removal of the solvent *in vacuo*  
15 afforded a red oil which was purified by flash chromatography, eluting with a gradient of 0-3% MeOH/ $\text{CHCl}_3$ . The title compound was isolated as an orange oil (0.65 g, 60%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.83 (s, 1H); 8.60 (d, 2H); 8.46 (d, 1H); 8.32 (d, 1H); 7.72 (t, 1H); 7.23 (d, 2H); 4.38 (s, 2H).

- 20       **(c) 2-Hydroxyimino-1-(3-nitrophenyl)-2-(4-pyridyl)acetophenone**  
The title compound was prepared using the same procedure as described in Example 10, step (c) except using 1-(3-nitrophenyl)-2-(4-pyridyl)acetophenone.

- 25       **(d) N-1-Hydroxy-2-(4-methylthiophenyl)-4-(3-nitrophenyl)-5-(4-pyridyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 2-hydroxyimino-1-(3-nitrophenyl)-2-(4-pyridyl)acetophenone and 4-(methylthio)benzaldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3/\text{MeOH}-d_4$ ):  $\delta$  8.55 (d, 2H); 8.43 (m, 1H); 8.15 (dd, 1H); 8.06 (d, 2H); 7.78 (d, 1H); 7.51 (m, 1H); 7.45 (d, 2H); 7.32 (m, 2H); 2.57 (s, 3H).

- 30       **Example 62b - 2-(4-Methylthiophenyl)-4-(3-nitrophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 1, except using N-1-hydroxy-2-(4-methylthiophenyl)-4-(3-nitrophenyl)-5-(4-pyridyl)imidazole: CIMS ( $\text{NH}_3$ ,  $m/z$ ): 389.1 ( $\text{M}^++\text{H}$ )

- 35       **Example 63 - 4-(3-Methanesulfonamidophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 29, except using 4-(3-aminophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 61 above]: ESMS ( $m/z$ ): 437.0 ( $\text{M}^++\text{H}$ ).

**Example 64 - 3-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl-1,2,4-oxadiazol-5(4H)-one** - To a mixture of 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide oxime (0.25 g, 0.67 mmol) [See Ex. 44

above] in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) and  $\text{Et}_3\text{N}$  (0.19 mL, 1.3 mmol) was added ethyl chloroformate (0.076 mL, 0.80 mmol) at rt. After 0.5 h at this temperature, the reaction mixture was poured into  $\text{H}_2\text{O}$ , extracted four times with  $\text{CH}_2\text{Cl}_2$  and once with 10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ . The organic extracts were combined and  
5 evaporated. The residue was purified by flash chromatography eluting with a solvent gradient of 2-4%  $\text{MeOH}/\text{CHCl}_3$ . Trituration with ether afforded a white solid (0.22 g, 73%). A portion of this compound (0.10 g, 0.22 mmol) was dissolved in  $\text{HOAc}$  (2.5 mL) and heated to reflux for 18 h. The reaction mixture was poured into  $\text{H}_2\text{O}$ , neutralized with concentrated  $\text{NH}_4\text{OH}$ , extracted with  
10  $\text{EtOAc}$  and evaporated. The residue was triturated sparingly with cold  $\text{EtOAc}$  to afford the title compound as a yellow solid (0.020 g, 23%): CIMS ( $\text{NH}_3$ ,  $m/z$ ): 400 ( $\text{M}^+ + \text{H}$ ).

**Example 65 - 4-(3-Acetamidophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same  
15 procedure as described in Example 6, except using 4-(3-aminophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 61 above]: ESMS ( $m/z$ ): 401 ( $\text{M}^+ + \text{H}$ ).

**Example 66 - 4-(4-Fluorophenyl)-1-N-hydroxy-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)imidazole** - (a) **2-Methyl isonicotinic acid** - The  
20 title compound was prepared using the same procedure as described in *Liebigs Ann. Chem.*, 1958, 613, 153: ESMS ( $m/z$ ): 138.0 ( $\text{M}^+ + \text{H}$ ).

(b) **Methyl 2-methylisonicotinate** - To an ice-cooled suspension of 1.32 g (9.62 mmol) of 2-methylisonicotinic acid in 20 mL of  $\text{MeOH}$  was added 1.47 mL (20.2 mmol) of thionyl chloride. The ice-bath was removed and the  
25 reaction was stirred at rt. After 22 h, the  $\text{MeOH}$  was evaporated and the residue was taken up in  $\text{H}_2\text{O}$ . The aqueous mixture was neutralized with saturated  $\text{NaHCO}_3$ , then extracted with  $\text{Et}_2\text{O}$ . The organic extracts were washed with saturated  $\text{NaCl}$ , dried over  $\text{MgSO}_4$ , then filtered through a bed of celite. Evaporation of solvent *in vacuo* afforded the title compound as a yellow  
30 liquid (0.89 g, 61%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.66 (d, 1H); 7.72 (s, 1H); 7.64 (d, 1H); 3.98 (s, 3H); 2.64 (s, 3H).

(c) **Methyl 4-fluorophenylacetate** - The title compound was prepared using the same procedure as described in Example 66, step (b) except using 4-fluorophenylacetic acid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.25 (dd, 2H); 7.02 (t, 2H); 3.71 (s,  
35 3H); 3.61 (s, 2H).

(d) **2-(4-Fluorophenyl)-1-[2-methyl-(4-pyridyl)]ethanone** - To a freshly prepared solution of  $\text{NaOMe}$  (3.0 M in  $\text{MeOH}$ ) was added a solution of methyl 2-methylisonicotinate (6.81 g, 45.1 mmol) in  $\text{MeOH}$  (10 mL). This was

followed by the dropwise addition of a solution of methyl 4-fluorophenylacetate (8.34 g, 49.6 mmol) in MeOH (10 mL). The MeOH was distilled off while heating the reaction mixture at 95 °C. After 17.5 h, the solid residue was cooled. Concentrated HCl (15 mL) was added, and the mixture was heated at reflux. After 4 h, the mixture was cooled then diluted with H<sub>2</sub>O. The aqueous mixture was washed with Et<sub>2</sub>O, adjusted to pH 5 with 1N NaOH, then adjusted to pH 8 with saturated NaHCO<sub>3</sub>. The alkaline aqueous was extracted with EtOAc. The EtOAc extracts were washed with saturated NaCl, then dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of solvent *in vacuo* afforded a red oil which was purified by column chromatography, eluting with a gradient of 0-3% MeOH/CHCl<sub>3</sub>. The title compound was isolated as a red oil (1.5 g, 15%).

(e) **2-(4-Fluorophenyl)-2-hydroxyimino-1-[2-methyl-(4-pyridyl)]ethanone** - The title compound was prepared using the same procedure as described in Example 10, step (c) except using 2-(4-fluorophenyl)-1-[2-methyl-(4-pyridyl)]ethanone: ESMS (*m/z*): 259 (M<sup>+</sup>+H).

(f) **4-(4-Fluorophenyl)-1-hydroxy-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)imidazole** - The title compound was prepared using the same procedure as described in Example 10, step (d) except using 2-(4-fluorophenyl)-2-hydroxyimino-1-[2-methyl-(4-pyridyl)]ethanone and 4-(methylthio)benzaldehyde: ESMS (*m/z*): 392 (M<sup>+</sup>+H).

**Example 67- 3-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-phenyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazole** - To a solution of 4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzamide oxime (0.25 g, 0.67 mmol) [See Ex. 44 above] in acetone (10 mL) was added pyridinium trifluoroacetate (0.39 g, 2.0 mmol). After heating at reflux for 18 h, the reaction mixture was poured into saturated aqueous NaHCO<sub>3</sub>, extracted with EtOAc and the organic phase was evaporated. The residue was purified by flash chromatography eluting with a solvent gradient of 2-10% MeOH/CHCl<sub>3</sub> to afford the title compound as a white solid (0.12 g, 43 %): CIMS (NH<sub>3</sub>, *m/z*): 414 (M<sup>+</sup>+H).

**Example 68 - N-Hydroxy-N-1-[4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl]ethyl] urea**

(a) **a-Methyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]benzyl alcohol** To a mixture of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (1.0 g, 2.9 mmol) [See Ex. 1 above] was added MeMgBr (3 M in Et<sub>2</sub>O, 4.0 mL, 12 mmol) at rt. The reaction mixture was heated at reflux for 1 h, poured into saturated aqueous NH<sub>4</sub>Cl, extracted with THF and the organic phase was evaporated. The residue was dissolved in MeOH (20 mL) and NaBH<sub>4</sub> (1.0 g, 26 mmol) was added. After 0.5

h at rt, the solvent was evaporated and the residue was purified by flash chromatography eluting with a solvent gradient of 1-10% MeOH/CHCl<sub>3</sub> to afford the title compound as a white solid (0.26 g, 25%): <sup>1</sup>H NMR (CDCl<sub>3</sub>/MeOH-d<sub>4</sub>): δ 8.37 (d, 2H); 7.79 (d, 2H); 7.4-7.2 (m, 6H); 6.99 (t, 3H); 4.76 (q, 1H); 1.35 (d, 3H).

(b) **N-Hydroxy-N-[1-[4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl]ethyl]urea** - To a mixture of a-Methyl-4-[4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzyl alcohol (0.25 g, 0.70 mmol), P(Ph)<sub>3</sub> (0.46 g, 1.75 mmol) and N,O-bis(benzyloxycarbonyl)hydroxylamine (0.48 g, 1.75 mmol) in THF (15 mL) was added DEAD (0.28 mL, 1.75 mmol) at rt. The reaction mixture was stirred at this temperature for 3 h and the solvent evaporated. The residue was partially purified by flash chromatography eluting with 1% MeOH/CHCl<sub>3</sub>. Methanol (25 mL) was added to this material and the mixture was cooled to -78 °C. Ammonia was bubbled in at this temperature for 15 min. The reaction mixture was warmed slowly to rt, stoppered and stirred at rt for 2 days. The solvent was evaporated and the residue was purified by flash chromatography eluting with a solvent gradient of 1-10% MeOH/CHCl<sub>3</sub>. The title compound was obtained as an off-white solid (0.43 g, 14%): FABMS (*m/z*): 418 (M<sup>+</sup>+H).

**Example 69 - N-Hydroxy-N-[4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl]methyl urea** - The title compound was obtained using the same procedure described in Example 68, except using 4-(4-fluorophenyl)-2-(4-hydroxymethyl)-5-(4-pyridyl)-1H-imidazole: FABMS (*m/z*): 418 (M<sup>+</sup>+H).

**Example 70 - 4-(3-Methylthiophenyl)-2-(4-morpholinomethylphenyl)-5-(4-pyridyl)-1H-imidazole** -

(a) **3-Methylthiobenzaldehyde** - The title compound was prepared using the same procedure as described by Campbell, J. R. in *J. Org. Chem.*, 1962, 27, 2207: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.95 (s, 1H); 7.72 (s, 1H); 7.61 (d, 1H); 7.45 (m, 2H); 2.53 (s, 3H).

(b) **1-(3-Methylthiophenyl)-2-(4-pyridyl)ethanol** - The title compound was prepared using the same procedure as described in Example 10, step (b) except using 3-(methylthio)benzaldehyde: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.33 (d, 2H); 7.0-7.5 (m, 6H), 4.87 (m, 1H); 2.96 (m, 2H); 2.45 (s, 3H).

(c) **1-(3-Methylthiophenyl)-2-(4-pyridyl)ethanedione** - To a solution of 1-(3-methylthiophenyl)-2-(4-pyridyl)ethanol (2.5 g, 10.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added a mixture of celite (4.4 g) and pyridinium dichromate (4.4 g, 20.4 mmol). After stirring for 12 h, the mixture was filtered through celite. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with a solvent gradient of 40-50% EtOAc/Hex to

provide the title compound (144 mg, 5.5%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.88 (br d, 2H); 7.85 (s, 1H); 7.78 (d, 2H); 7.67(d, 1H); 7.56 (d, 1H); 7.44 (t, 1H); 2.55 (s, 3H).

5 (d) **4-Morpholinomethylbenzaldehyde diethyl acetal** - The title compound was prepared using the same procedure as described by Borch, R. F., Bernstein, M. D., and Durst, H. D. in *J. Am. Chem. Soc.*, **1971**, *93*, 2897 except using the diethyl acetal:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.41 (d, 2H); 7.32 (d, 2H); 5.48 (s, 1H); 3.3-3.8 (m, 10H); 2.43 (br s, 4H); 1.25 (t, 6H).

10 (e) **4-(3-Methylthiophenyl)-2-(4-morpholinomethylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13 except using 1-(3-methylthiophenyl)-2-(4-pyridyl)-ethanedione and 4-morpholinomethylbenzaldehyde diethyl acetal:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.47 (d, 2H); 8.02 (d, 2H); 7.3-7.9 (m, 8H); 3.72 (t, 4H); 3.54 (s, 2H); 2.44 (br s, 4H); 2.38 (s, 3H).

15 **Example 71 - 4-(3-Methylsulfinylphenyl)-2-(4-morpholinomethylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described for Example 20, except using 4-(3-methylthiophenyl)-2-(4-morpholinomethylphenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 70 above]:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.38 (d, 2H);  
20 7.92 (d, 2H); 7.1-7.6 (m, 8H); 3.76 (t, 4H); 3.59, (s, 2H); 2.73 (s, 3H); 2.52 (br s, 4H).

**Example 72 - 4-(3-Methanesulfonamidophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20, except  
25 using 4-(3-methanesulfonamido-phenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 63 above]: CIMS ( $\text{NH}_3$ ,  $m/z$ ): 453.3 ( $\text{M}^+ + \text{H}$ ).

**Example 73 - 2-(4-Ethylthiophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-ethylthiobenzaldehyde: mp 203-  
30 205 °C.

**Example 74 - 2-(4-Ethylsulfinylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 20, except using 2-(4-ethylthiophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole [See Ex. 73 above]: mp 240 °C.

35 **Example 75 - 4-(4-Fluorophenyl)-2-[(4-(4-methyl-1-piperziny)-sulfonyl-phenyl)-5-(4-pyridyl)-1H-imidazole**

(a) **Ethyl [4-(4-methyl piperaziny) sulfonamido] benzoate** - A mixture of 4-chlorosulfonyl benzoic acid (5.0 g, 22.67 mmol), N-methyl



piperazine (25 mL) and MeOH (5 mL) was stirred for 18 h and ether (200 mL) was added to the mixture. The crystalline solid precipitate was filtered and washed with ether (200 mL). The solid was suspended in 20% ethanolic HCl and the mixture was heated at reflux until a homogeneous solution was attained (about 2 h). The solution was cooled to rt, concentrated, and the residue was partitioned between sat. NaHCO<sub>3</sub> and EtOAc. The organic extract was dried and concentrated to yield the title compound (5.8 g 80%).

(b) **4-(4-Methyl piperazinyl) sulfonamido benzyl alcohol** - The title compound was prepared using the same procedure as described in Example 78, step (b) except using ethyl [4-(4-methyl piperazinyl) sulfonamido] benzoate.

(c) **4-(4-Methyl piperazinyl) sulfonamido benzaldehyde** - To a solution of oxalyl chloride (1.06 mL, 12.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added DMSO (1.8 mL, 25.4 mmol) at -60 °C and the mixture was stirred for 25 min. A solution of 4-(4-methyl piperazinyl) sulfonamido benzyl alcohol (3.0 g, 10.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and DMSO (5 mL) was added and the mixture was stirred for 1.5 h at -60 °C. Triethylamine (7.4 mL) was added and the mixture was partitioned between brine and EtOAc. The organic extract was concentrated, then purified by flash chromatography to yield the title compound (1.0 g, 33%).

(d) **4-(4-Fluorophenyl)-2-[4-(4-methyl piperazinyl) sulfonamido phenyl]-5-(4-pyridyl)-1H-imidazole** - The title compound was prepared using the same procedure as described in Example 13, except using 4-(4-methyl piperazinyl) sulfonamido benzaldehyde: mp. 74-76 °C.

Example 76 - **4-(4-Fluorophenyl)-2-[4-(N-methylmethanesulfonamido)-methylphenyl]-5-(4-pyridyl)-1H-imidazole**

(a) **Methyl 4-[(methanesulfonamido)methyl]benzoate** - To a suspension of 4-(aminomethyl)benzoic acid (10 g, 66 mmol) in MeOH (100 mL) at 0 °C was added SOCl<sub>2</sub> (5.3 mL, 73 mmol) dropwise. The ice bath was removed and the reaction stirred at rt overnight. After heating the reaction at reflux for 4 h, the solvent was evaporated. The residue was suspended in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C and triethylamine (25 mL) was added, followed by the dropwise addition of methanesulfonyl chloride (7.75 mL, 100 mmol). The reaction was stirred at rt for 1 h, poured into ice H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude product was flash chromatographed on silica gel eluting with 1% MeOH/CHCl<sub>3</sub>. The title compound was isolated as a white solid (11.8 g, 74 %): <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03 (d, 2H); 7.42 (d, 2H); 4.9 (br t, 1H); 4.38 (d, 2H); 3.92 (s, 3H); 2.89 (s, 3H).

**(b) Methyl 4-[(N-Methylmethanesulfonamido)methyl]benzoate**

- To a mixture of methyl 4-[(methanesulfonamido)methyl]benzoate (5 g, 20.6 mmol) in MeOH (100 mL) at rt was added  $K_2CO_3$  (2.9 g, 21 mmol). Methyl iodide (7 mL, 16 g, 112 mmol) was added and the mixture stirred overnight.

5 The reaction was filtered and the solid washed with  $CHCl_3$ /MeOH. The combined filtrates were evaporated and the residue was purified by flash chromatography on eluting with 0-5% MeOH/  $CHCl_3$ . The title compound was isolated as a white solid (4.9 g, 94%):  $^1H$  ( $CDCl_3$ ):  $\delta$  8.08 (d, 2H); 7.48 (d, 2H); 4.41 (s, 1H); 3.97 (s, 3H); 3.91 (s, 3H); 2.83 (s, 3H).

**10 (c) 4-[(N-Methylmethanesulfonamido)methyl]benzyl alcohol-**

The title compound was prepared using the same procedure as described in Example 78, step (b) except using methyl 4-[(N-methylmethanesulfonamido)methyl]benzoate:  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.34 (m 4H); 4.68 (s, 2H); 4.29 (s, 2H); 2.83 (s, 3H); 2.74 (s, 3H).

**15 (d) 4-[(N-Methylmethanesulfonamido)methyl]benzaldehyde-**

The title compound was prepared using the same procedure as described in Example 78, step (c) except using 4-[(N-methylmethanesulfonamido)methyl]benzyl alcohol:  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  10.02 (s, 1H); 7.9 (d, 2H); 7.54 (d, 2H); 4.4 (s, 2H); 2.9 (s, 3H); 2.81 (s, 3H).

**20 (e) 4-(4-Fluorophenyl)-2-[4-(N-methylmethanesulfonamido)-methylphenyl]-5-(4-pyridyl)-1H-imidazole -** The title compound was prepared using the same procedure as described in Example 13, except using 4-[(N-methylmethanesulfonamido)methyl]benzaldehyde: mp 222-224 °C.  
**Example 77 - Diethyl [1-methyl-4-phenyl-5-(4-pyridyl)-imidazol-2-yl]methoxy]methylphosphonate**

25 **(a) N-Methyl-N-[4-picoly]formamide** - To a solution of 4-picoly chloride-HCl (15 g, 91.4 mmol) and N-methylformamide (53.4 mL, 914 mmol) in 300 mL of THF was added 80% NaH in mineral oil (5.48 g, 183 mmol). After stirring at rt for 18 h the mixture was quenched with ice water and partitioned between  $CH_2Cl_2$  and  $H_2O$ . The organic extract was washed with aqueous NaCl and dried over  $MgSO_4$ . The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 50:1  $CH_2Cl_2$ /MeOH. The title compound was obtained as a pale yellow oil (10.5 g, 76%): ESMS ( $m/z$ ): 151 ( $M^+ + H$ ).

35 **(b) 1-Methyl-4-phenyl-5-[4-pyridyl]imidazole** - To a solution of di-*iso*-propyl-amine (11.2 mL, 79.9 mmol) in 150 mL of THF at -78 °C was added *n*-butyllithium (31.9 mL of 2.5 M solution, 79.9 mmol). To the resulting mixture was added a solution of N-methyl-N-[4-picoly]formamide (10 g, 66.5 mmol) in THF. The resulting orange-brown solution was stirred

at -78 °C for 20 min, at which time benzonitrile (13.6 mL, 133 mmol) was added. The resulting dark brown mixture was allowed to warm to rt and stirred for 1 h, heated to reflux for 4 h, and then cooled to rt and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic extract was washed with aqueous NaCl and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The title compound was obtained as a light tan solid (5.83 g, 37%); mp 158-159 °C.

(c) **2-Formyl-1-methyl-4-phenyl-5-[4-pyridyl]imidazole** - To a solution of 1-methyl-4-phenyl-5-[4-pyridinyl]imidazole (0.275 g, 1.17 mmol) in THF at -78 °C was added n-butyllithium (0.56 mL of 2.5 M solution, 1.40 mmol). The resulting red-orange solution was allowed to stir at -78 °C for 0.5 h when DMF (0.18 mL, 2.34 mmol) was added. The mixture was allowed to warm to rt and stir for 4 h, then quenched with ice water and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic extract was washed with aqueous NaCl and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* and the residue was purified by flash chromatography eluting with 50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The title compound was obtained as a white solid (0.187 g, 61%); mp 167-168 °C.

(d) **2-Hydroxymethyl-1-methyl-4-phenyl-5-(4-pyridyl)imidazole** - To a solution of 2-formyl-1-methyl-4-phenyl-5-[4-pyridyl]imidazole (0.830 g, 3.15 mmol) in MeOH at 0 °C was added NaBH<sub>4</sub> (0.143 g, 3.78 mmol). The mixture was stirred at rt for 0.5 h when the solvent was evaporated *in vacuo* and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic extract was washed with aqueous NaCl and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* and the residue was purified by flash chromatography eluting with 25:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The title compound was obtained as a white solid (0.608 g, 73%); mp 236-238 °C.

(e) **Diethyl [1-methyl-4-phenyl-5-(4-pyridyl)imidazol-2-yl]methoxy]-methyl-phosphonate** - To a suspension of 80% NaH in mineral oil (0.013 g, 0.452 mmol) in DMF at 0 °C was added 1-methyl-2-hydroxymethyl-4-phenyl-5-[4-pyridinyl]imidazole (0.100 g, 0.377 mmol) in DMF. The resulting bright yellow solution was stirred at 0 °C for 0.5 h when diethyl chloromethylphosphonate (0.070 mL, 0.452 mmol) dissolved in 0.079 mL of HMPA was added. The resulting mixture was stirred at 0 °C for 15 min and then warmed to rt. After 5 h, the solution was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic extract was washed with aqueous NaCl and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The title compound was obtained as a light amber oil (0.088 g, 56%); ESMS (*m/z*): 416 (M<sup>+</sup>+H).

**Example 78- 4-(4-Fluorophenyl)-2-[4-(methanesulfonamido)-methylphenyl]-5-(4-pyridyl)-1H-imidazole - (a) Methyl 4-[(methanesulfonamido)methyl]-benzoate** - The title compound was prepared using the same procedure as described in Example 76, step (a).

5       **(b) 4-[(Methanesulfonamido)methyl]benzyl alcohol** - To a mixture of methyl 4-[(methanesulfonamido)methyl]benzoate (3.6 g, 15 mmol) in THF (150 mL) was added  $\text{LiAlH}_4$  (1 M in THF, 30 mL, 30 mmol). The reaction mixture was stirred at rt for 1 h and poured into 10% MeOH/ $\text{CHCl}_3$  containing silica gel. The solids were removed by filtration, washed with 10%  
10       MeOH/ $\text{CHCl}_3$  and the combined washings were evaporated to yield the title compound as a white solid (2.6 g, 80%).

**(c) 4-[(Methanesulfonamido)methyl]benzaldehyde** - To a solution of 4-[(methanesulfonamido)methyl]benzyl alcohol (1.0 g, 4.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added pyridinium chlorochromate (1.5 g, 7.0 mmol). The reaction  
15       mixture was stirred for 1 h at rt and poured through a pad of silica gel eluting with 2% MeOH/ $\text{CHCl}_3$ . The title compound was isolated as a tan solid (1.0 g, 100 %):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.03 (s, 1H); 7.88 (d, 2H); 7.57 (d, 2H); 4.79 (br s, 1H); 4.43 (d, 2H); 2.93 (s, 3H).

**(d) 4-(4-Fluorophenyl)-2-[4-(methanesulfonamido)methylphenyl]-5-(4-pyridyl)-1H-imidazole** - The title compound [also prepared in Example 32] was prepared using the same procedure as described in Example 13, except  
20       using 4-[(methanesulfonamido)methyl]benzaldehyde.

**Example 79 - 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole**

25       **(a) 1-(t-Butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone** - To a  $-20^\circ\text{C}$  solution of diisopropylamine (64.4 mL, 0.46 mol) and THF (120 mL) was added 207.8 mL (0.52 mol, 2.5 M solution in hexanes) of n-butyllithium dropwise over 15 min. The temperature was lowered to  $-15^\circ\text{C}$  and the mixture was stirred for 0.5 hr. The solution was cooled to  $-20^\circ\text{C}$  and 98.14 g (0.44 mol) of 4-(t-butyldimethylsilyloxy)methyl pyridine was  
30       added dropwise over 20 min. After stirring at  $-20^\circ\text{C}$  for 45 min, a solution of 4-fluoro-N-methoxy-N-methylbenzamide (84.5 g, 0.46 mol) [See Ex. 10, step (a)] in THF (90 mL) was added dropwise over 0.5 hr. Once the addition was complete, the ice bath was removed and the reaction mixture was warmed to  $0^\circ\text{C}$  for 1 hr, then stirred at rt for 1.5 hr. The mixture was poured into a solution  
35       of  $\text{NH}_4\text{Cl}$  (98 g) and  $\text{H}_2\text{O}$  (500 mL), then extracted with EtOAc (3 x 250 mL). The EtOAc extracts were washed with  $\text{H}_2\text{O}$  and saturated NaCl, then dried over  $\text{MgSO}_4$ . Evaporation of the solvent *in vacuo* afforded the title compound as an amber oil (114.2 g, 75%).

(b) 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole - To a solution of 1-(t-butyltrimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone (6.3 g, 18.3 mmol) in glacial acetic acid (125 mL) was added anhydrous copper (II) acetate (6.6 g, 36.5 mmol), ammonium acetate (14 g, 183 mmol) and 4-(methylthio)benzaldehyde (3.5 g, 22.9 mmol) and the mixture was heated at reflux. After 1 hr, the reaction was cooled then poured into a mixture of conc.  $\text{NH}_4\text{OH}$  (175 mL), ice (100 mL) and EtOAc (100 mL). The resulting mixture was stirred for 15 min, then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined EtOAc extracts were washed with saturated NaCl and dried over  $\text{MgSO}_4$ . Evaporation of solvent *in vacuo* gave an oil which was taken up in acetone. 3 N HCl was added dropwise to adjust the pH to 2-3, and the resulting solid was filtered. The title compound [also prepared in Ex. 17 as the free base] was isolated as the yellow hydrochloride salt (3.7 g, 51%).

15 **Example 80 - 2-[4-[(N-Benzyl-N-methyl) aminomethyl]phenyl]4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole**

(a) 4-[(N-benzyl-N-methyl)aminomethyl]benzaldehyde diethylacetal - To 62.4 g (0.30 mol) of terephthalaldehyde monodiethyl acetal was added 32.1 g (0.30 mol) of benzyl amine and 500 mL toluene. The resulting solution was heated at reflux using a Dean-Stark trap. After 1 hour the solution was cooled and concentrated to give a light yellow oil (89.1 g). The oil was dissolved in 900 mL of EtOAc and 2.0 g of 5% palladium on charcoal was added. The mixture was hydrogenated on a Parr hydrogenation apparatus under 37 psi hydrogen pressure. The mixture was shaken for 1 hour at rt. The bottle was vented and 34.4 mL (0.42 mol) of 37.5% formaldehyde solution (aqueous) was added. The bottle was repressurized with 33 psi hydrogen and the mixture was shaken for 17 hours at rt. The bottle was vented and the reaction mixture was filtered and the filtrate concentrated to a nearly colorless oil (93.9 g). Vacuum distillation gave 71.4 g (76%) of 4-(N-methyl-N-benzyl)aminomethylbenzaldehyde diethylacetal: bp (30 torr) 212-234 °C.

(b) 2-[4-[(N-Benzyl-N-methyl) aminomethyl]phenyl]4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole - The title compound [also prepared in Ex. 36] was prepared as described in Example 13, except using 4-[(N-benzyl-N-methyl)aminomethyl]benzaldehyde diethylacetal.

### BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

1. IL-1 - Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al.*, J Immunol, 132, 936 (1984). These monocytes ( $1 \times 10^6$ ) were plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional 24h. At the end of this period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, 84, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, 6 (1), 1-12 (1990) (ELISA assay). Compounds of formula (I) were shown to be inhibitors of *in vitro* IL-1 produced by human monocytes.
2. TNF - Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J Immunol, 132(2), 936 (1984). The monocytes were plated at a density of  $1 \times 10^6$  cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells were incubated for 45 minutes in the presence or absence of a test compound at 1nM-10µM dose ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium was 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopolysaccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) was then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO<sub>2</sub> incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant was then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, 147, 4307. Compounds of formula (I) were shown to be inhibitors of *in vitro* TNF production.

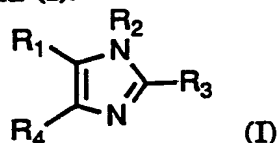
IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid

metabolism inhibition, further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

- 5 3. IL-8 - Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) were maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells were then diluted 20-fold before being plated (250 $\mu$ l) into  
10 gelating coated 96-well plates. Prior to use, culture medium was replaced with fresh medium (200 $\mu$ l). Buffer or test compound (25 $\mu$ l, at concentrations between 1 and 10 $\mu$ M) was then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO<sub>2</sub>. At the end of the incubation period, supernatant  
15 was removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data were presented as mean value (ng/ml) of multiple samples based on the standard curve. IC<sub>50</sub>'s where appropriate were generated by non-linear regression analysis. The compounds of formula (I), examples 5, 8b and 9, demonstrated a dose  
20 dependent reduction in the production of IL-8 (a 50-65% inhibition of IL-8).

# Claims

1. A compound of formula (I):



5 wherein

R<sub>1</sub> is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from C<sub>1-4</sub> alkyl, halo, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, NH<sub>2</sub>, mono- or di-C<sub>1-6</sub> alkylamino or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>22</sub>;

R<sub>2</sub> is R<sub>8</sub> or -OR<sub>12</sub>;

R<sub>3</sub> is -X<sub>a</sub>P(Z)(X<sub>b</sub>R<sub>13</sub>)<sub>2</sub> or an optionally substituted aryl or heteroaryl

15 group Q;

X<sub>a</sub> is -NR<sub>8</sub>-, -O-, -S- or a C<sub>1-10</sub> alkylene chain optionally substituted by C<sub>1-4</sub> alkyl and optionally interrupted by -NR<sub>8</sub>-, -O- or -S-;

X<sub>b</sub> is -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>-, -NR<sub>8</sub>-, -O- or -S-;

Z is oxygen or sulfur;

20 n is 0 or an integer from 1 to 10;

R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, C(Z)NR<sub>7</sub>R<sub>17</sub>, C(Z)OR<sub>23</sub>, - (CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>COR<sub>36</sub>, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>36</sub>, halo-substituted-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl, -ZC(Z)R<sub>36</sub>, -NR<sub>10</sub>C(Z)R<sub>23</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>10</sub>R<sub>20</sub> and which, for other positions of substitution, is halo, cyano, C(Z)NR<sub>16</sub>R<sub>26</sub>, C(Z)OR<sub>8</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>COR<sub>8</sub>, S(O)<sub>m</sub>R<sub>8</sub>, OR<sub>8</sub>, halo-substituted-C<sub>1-4</sub> alkyl, -C<sub>1-4</sub> alkyl, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -ZC(Z)R<sub>8</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>16</sub>R<sub>26</sub>;

25 m is 0, 1 or 2;

R<sub>5</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>7</sub>R<sub>17</sub>, excluding -SR<sub>5</sub> being -SNR<sub>7</sub>R<sub>17</sub> and -SOR<sub>5</sub> being -SOH or ;

R<sub>6</sub> is C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or C<sub>3-5</sub> cycloalkyl;

35



- R<sub>7</sub> and R<sub>17</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl or R<sub>7</sub> and R<sub>17</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>22</sub>;
- R<sub>8</sub> is hydrogen, heterocyclyl, heterocyclalkyl or R<sub>11</sub>;
- R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl;
- R<sub>11</sub> is C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- R<sub>12</sub> is hydrogen, -C(Z)R<sub>13</sub> or optionally substituted C<sub>1-4</sub> alkyl, aryl or aryl-C<sub>1-4</sub> alkyl;
- R<sub>13</sub> is hydrogen, C<sub>1-10</sub> alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- R<sub>16</sub> and R<sub>26</sub> is each independently selected from hydrogen or optionally substituted C<sub>1-4</sub> alkyl, aryl or aryl-C<sub>1-4</sub> alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>12</sub>;
- R<sub>22</sub> is R<sub>10</sub> or C(Z)-C<sub>1-4</sub> alkyl;
- R<sub>23</sub> is C<sub>1-4</sub> alkyl, halo substituted C<sub>1-4</sub> alkyl, or C<sub>3-5</sub> cycloalkyl;
- R<sub>36</sub> is hydrogen or R<sub>23</sub>;
- or a pharmaceutically acceptable salt thereof;
- and excluding 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-pyridyl)imidazole.

2. A compound as claimed in claim 1 wherein R<sub>1</sub> is optionally substituted 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinolyl, 1-imidazolyl or 1-benzimidazolyl.
3. A compound as claimed in claim 1 or 2 wherein R<sub>2</sub> is hydrogen or C<sub>1-10</sub> alkyl.
4. A compound as claimed in any one of claims 1 to 3 wherein, in R<sub>3</sub>, the group Q comprises an optionally substituted phenyl, pyrrolyl, pyridyl or pyrimidyl moiety.

5. A compound as claimed in any one of claims 1 to 4 wherein Q is substituted by up to three substituents  $Y_1$  each of which is independently selected from  $C_{1-5}$  alkyl, halo-substituted  $C_{1-5}$  alkyl, halogen,  $-X_a-P(Z)-(X_bR_{13})_2$  or  $-(CR_{10}R_{20})_nY_2$  wherein  $Y_2$  is  $-OR_8$ ,  $-NO_2$ ,  $-S(O)_mR_{11}$ ,  $-SR_8$ ,  $-S(O)_mOR_8$ ,  $-S(O)_mNR_8R_9$ ,  $-NR_8R_9$ ,  $-O(CR_{10}R_{20})_nNR_8R_9$ ,  $-C(O)R_8$ ,  $-CO_2R_8$ ,  $-CO_2(CR_{10}R_{20})_nCONR_8R_9$ ,  $-ZC(O)R_8$ ,  $-CN$ ,  $-C(Z)NR_8R_9$ ,  $-NR_{10}C(Z)R_8$ ,  $-C(Z)NR_8OR_9$ ,  $-NR_{10}C(Z)NR_8R_9$ ,  $-NR_{10}S(O)_mR_{11}$ ,  $-N(OR_{21})C(Z)NR_8R_9$ ,  $-N(OR_{21})C(Z)R_8$ ,  $-C(=NOR_{21})R_8$ ,  $-NR_{10}C(=NR_{15})SR_{11}$ ,  $-NR_{10}C(=NR_{15})NR_8R_9$ ,  $-NR_{10}C(=CR_{14}R_{24})SR_{11}$ ,  $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$ ,  $-NR_{10}C(O)C(O)NR_8R_9$ ,  $-NR_{10}C(O)C(O)OR_{10}$ ,  $-C(=NR_{13})NR_8R_9$ ,  $-C(=NOR_{13})NR_8R_9$ ,  $-C(=NR_{13})ZR_{11}$ ,  $-OC(Z)NR_8R_9$ ,  $-NR_{10}S(O)_mCF_3$ ,  $-NR_{10}C(Z)OR_{10}$ , 5-( $R_{18}$ )-1,2,4-oxadiazol-3-yl or 4-( $R_{12}$ )-5-( $R_{18}R_{19}$ )-4,5-dihydro-1,2,4-oxadiazol-3-yl;  $m'$  is 1 or 2;  $n'$  is 1 to 10;  $R_9$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-7}$  cycloalkyl,  $C_{5-7}$  cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or  $R_8$  and  $R_9$  may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>12</sub>;  $R_{14}$  and  $R_{24}$  is each independently selected from hydrogen, alkyl, nitro or cyano;  $R_{15}$  is hydrogen, cyano,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl or aryl;  $R_{18}$  and  $R_{19}$  is each independently selected from hydrogen,  $C_{1-4}$  alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote oxygen or sulfur; and  $R_{21}$  is hydrogen, a pharmaceutically acceptable cation, alkyl, cycloalkyl, aryl, aryl $C_{1-4}$ alkyl, heteroaryl, heteroaryl $C_{1-4}$ alkyl, heterocyclyl, aroyl,  $C_{1-10}$ alkoyl.

6. A compound as claimed in claim 5 wherein the substituent  $Y_1$  is selected from halogen,  $C_{1-5}$  alkyl and  $-(CR_{10}R_{20})_nY_2$  wherein  $Y_2$  is  $-OR_8$ ,  $-NO_2$ ,  $-S(O)_mR_{11}$ ,  $-SR_8$ ,  $-S(O)_mNR_8R_9$ ,  $-NR_8R_9$ ,  $-O(CR_{10}R_{20})_nNR_8R_9$ ,  $-C(O)R_8$ ,  $-CO_2R_8$ ,  $-CO_2(CR_{10}R_{20})_nCONR_8R_9$ ,  $-CN$ ,  $-C(Z)NR_8R_9$ ,  $-NR_{10}S(O)_mR_{11}$ ,  $-NR_{10}C(Z)R_8$ ,  $-NR_{10}C(Z)NR_8R_9$ ,  $-N(OR_{21})C(Z)NR_8R_9$ ,  $-C(Z)NR_8OR_9$ ,  $-NR_{10}C(=NR_{15})NR_8R_9$ ,  $-C(=NOR_{13})NR_8R_9$ , 5-( $R_{18}$ )-1,2,4-oxadiazol-3-yl or 4-( $R_{12}$ )-5-( $R_{18}R_{19}$ )-4,5-dihydro-1,2,4-oxadiazol-3-yl.

7. A compound as claimed in claim 6 wherein the group Q has one substituent  $Y_1$  which is selected from  $-(CR_{10}R_{20})_nY_2$  wherein:  $n$  is 0,

- 1, 2 or 3, and Y<sub>2</sub> is -OR<sub>8</sub>, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sub>11</sub>, -SR<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>, -C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -C(Z)NR<sub>8</sub>OR<sub>9</sub>, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, -N(OR<sub>21</sub>)C(Z)NR<sub>8</sub>R<sub>9</sub>,  
 5 -C(=NOR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(=NR<sub>15</sub>)NR<sub>8</sub>R<sub>9</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadizaol-3-yl and 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl.
8. A compound as claimed in claim 7 wherein, in Y<sub>1</sub>, n is 0 or 1 and Y<sub>2</sub> is -OH, -S(O)<sub>m</sub>R<sub>11</sub>, -SR<sub>8</sub>, -NR<sub>8</sub>R<sub>9</sub>, -CO<sub>2</sub>R<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>,  
 10 -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadizaol-3-yl or 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl.
9. A compound as claimed in any one of claims 1 to 8 wherein, in R<sub>4</sub>,  
 15 a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent is halogen, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>36</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>16</sub>R<sub>26</sub>, or -NR<sub>10</sub>C(Z)R<sub>8</sub> and a substituent for another positions of substitution is selected from halogen, -S(O)<sub>m</sub>R<sub>8</sub>, -OR<sub>8</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>NR<sub>16</sub>R<sub>26</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub> or -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>.
- 20 10. A compound as claimed in any one of claims 1 to 9 wherein R<sub>1</sub> is 4-pyridyl, 2-alkyl-4-pyridyl or 4-quinolyl; R<sub>2</sub> is hydrogen or methyl; R<sub>3</sub> is phenyl or phenyl substituted, preferably at the 4-position, with a substituent selected from -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub> wherein Y<sub>2</sub> is wherein n is 0,  
 25 1 2 or 3 and Y<sub>2</sub> is -OR<sub>8</sub>, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sub>11</sub>, -SR<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>, -C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>, -C(Z)NR<sub>8</sub>OR<sub>9</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, -C(=NOR<sub>13</sub>)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)NR<sub>8</sub>R<sub>9</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadizaol-3-yl, 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl or a 3,5-dimethyl- or 3,5-  
 30 dibromo-4-hydroxyl grouping; and R<sub>4</sub> is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C<sub>1-4</sub> alkoxy, methane-sulfonamido or acetamido.
11. A compound of formula (I) as defined in claim 1 selected from:  
 35 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;  
 4-(4-Fluorophenyl)-2-(4-ethylthiophenyl)-5-(4-pyridyl)imidazole;  
 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;  
 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

- 4-(4-Fluorophenyl)-2-(4-ethylsulfinylphenyl)-5-(4-pyridyl)imidazole;  
 4-(3-Chlorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;  
 2-[4-(N-Methyl-N-benzyl)aminomethylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole;  
 5 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylthiophenyl)-imidazole;  
 4-(4-Fluorophenyl)-5-[4-(2-methylpyridyl)]-2-(4-methylsulfinylphenyl)-imidazole;  
 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-quinolyl)imidazole;  
 10 2-[4-(N-Morpholino)methylphenyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-imidazole; or  
 a pharmaceutically acceptable salt thereof.

12. A process for preparing a compound of formula (I) as defined in  
 15 any one of claims 1 to 11 which process comprises:

(i) condensing an  $\alpha$ -diketone of formula (II):



wherein  $R_1$  and  $R_4$  are as hereinbefore defined, or an equivalent thereof,

- 20 with an aldehyde of the formula (III):



wherein  $R_3$  is as hereinbefore defined, or an equivalent thereof, and, if necessary, with ammonia or a source thereof, under imidazole-ring forming conditions;

- 25 (ii) treating an  $\alpha$ -hydroxyketone compound of formula (IIA):



- wherein one of  $R'$  and  $R''$  is  $R_1$  and the other is  $R_4$ , a suitably protected derivative thereof or the  $\alpha$ -hydroxy-oxime or  $\alpha$ -haloketone derivative thereof, with an oxidising agent capable of converting said compound  
 30 into the corresponding  $\alpha$ -diketone, in the presence of an aldehyde of formula (III) or an equivalent thereof, and a source of ammonia;

(iii) treating an amidine of formula (IV):



- wherein  $R_2$  and  $R_3$  are as hereinbefore defined, or a salt thereof, with  
 35 a reactive ester of an  $\alpha$ -hydroxyketone of formula (IIA) or the corresponding  $\alpha$ -haloketone, in an inert solvent, at a moderately elevated temperature and, if necessary, in the presence of a suitable condensation agent;

(iv) treating an iminoether of formula (V):



wherein  $R_3$  is as hereinbefore defined and  $R$  is  $C_{1-10}$  alkyl, aryl or aryl  $C_{1-4}$  alkyl, with an  $\alpha$ -aminoketone of the formula (VI):



- 5 wherein one of  $R'$  and  $R''$  is  $R_1$  and the other is  $R_4$  in a suitable solvent;

(v) treating the anion of an amide of formula (VII):



- 10 wherein  $R_1$  and  $R_3$  are as hereinbefore defined and  $R_2$  is as hereinbefore defined other than hydrogen, with:

(a) a nitrile of the formula (VIII):



wherein  $R_4$  is as hereinbefore defined, or

(b) an excess of an acyl halide, of the formula (IX):



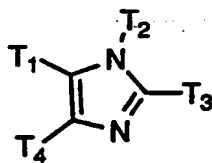
15 wherein  $R_4$  is as hereinbefore defined and  $Hal$  is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia;

(vi) treating a compound of formula (X):



20 wherein  $R'$ ,  $R''$  and  $R_4$  are as hereinbefore defined and  $X_c$  is  $O$  or  $NH$ , with a source of ammonia, or cyclising the corresponding Schiff's base, formed by treating the compound of formula (X) with an amine  $R_2NH_2$ ;

- 25 (vii) coupling a suitable derivative of a compound of formula (XI):



(XI)

- 30 wherein:  $T_2$  is a nitrogen protecting group or  $R_2$ , other than hydrogen; and  $T_1$  is hydrogen,  $T_3$  is  $Q$  and  $T_4$  is  $R_4$ ;  $T_1$  is  $R_1$ ,  $T_3$  is hydrogen and  $T_4$  is  $R_4$ ; or  $T_1$  is  $R_1$ ,  $T_3$  is  $Q$  and  $T_4$  is hydrogen, in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $Q$  are as hereinbefore defined; with: (i) when  $T_1$  is hydrogen, a suitable derivative of the heteroaryl ring  $R_1H$ , under ring coupling conditions, to effect coupling of the heteroaryl ring  $R_1$  to the imidazole nucleus at position 5; (ii) when  $T_3$  is
- 35 hydrogen, a suitable derivative of the aryl or heteroaryl ring  $QH$ ,

- under ring coupling conditions, to effect coupling of the ring Q to the imidazole nucleus at position 2; or (iii) when T<sub>4</sub> is hydrogen, a suitable derivative of the aryl ring R<sub>4</sub>H, under ring coupling conditions, to effect coupling of the aryl ring R<sub>4</sub> to the imidazole nucleus at position 4;
- 5 (viii) treating a compound of formula (XI), wherein T<sub>1</sub> is hydrogen, with an N-acyl heteroaryl salt, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate is then
- 10 subjected to oxidative-deacylation conditions; and
- thereafter and if necessary carrying out all or any of the additional steps of removing a protecting group, transforming an initially obtained compound of formula (I) into a further compound of formula (I) or forming a pharmaceutically acceptable salt.
- 15
13. A compound of formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in therapy.
- 20
14. The use of a compound of formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cytokine-mediated disease state.
- 25
15. A pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

# INTERNATIONAL SEARCH REPORT

T/US 93/00674

International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D401/04; C07D403/04; A61K31/44; A61K31/47 A61K31/505			
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<b>II. FIELDS SEARCHED</b> Minimum Documentation Searched <sup>7</sup>	
Classification System Int.Cl. 5	Classification Symbols C07D ; C07F

Documentation Searched other than Minimum Documentation  
to the extent that such Documents are included in the Fields Searched<sup>8</sup>

<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		Relevant to Claim No. <sup>13</sup>
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	
X	DE, A, 2 221 546 (CIBA-GEIGY A.G.) 16 November 1972 see claims 1, 31-33, 36, 38, 43, 49, 51 see claims 52, 61-64 & US, A, 3 929 807 cited in the application	1-7, 12-15
X	US, A, 3 772 441 (JOSEPH GEORGE LOMBARDINO) 13 November 1973 see claims & US, A, 3 707 405 cited in the application	1-5, 12-15
A	EP, A, 0 011 111 (SMITH KLINE CORPORATION) 28 May 1980 see claims	1, 13-15

<sup>10</sup> Special categories of cited documents:

- <sup>"A"</sup> document defining the general state of the art which is not considered to be of particular relevance
- <sup>"E"</sup> earlier document but published on or after the international filing date
- <sup>"L"</sup> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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<b>IV. CERTIFICATION</b>	
Date of the Actual Completion of the International Search <div style="text-align: center;">14 JUNE 1993</div>	Date of Mailing of this International Search Report <div style="text-align: center;">21. 06. 93</div>
International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;">HENRY J.C.</div>

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
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